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Proposed Re-evaluation Decision PRVD2016-18

Cypermethrin

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Overview

General Introduction

In Canada, pesticides are regulated under the *Pest Control Products Act*, administered by Health Canada's Pest Management Regulatory Agency (PMRA). All pesticides are registered (i.e. approved) if a rigorous scientific assessment indicates that the health and environmental risks are acceptable and the products have value. The *Pest Control Products Act* also contains provisions for post-market reviews of registered pesticides namely, re-evaluation and special reviews, to assess whether pesticides continue to meet Health Canada's health and environmental standards, and whether they can continue to be used in Canada.

As part of the decision making process, before making a final decision, the PMRA consults with the members of the public and other interested stakeholders on all proposed major decisions such as new registrations, re-evaluations and special reviews. The PMRA encourages the public and stakeholders to participate in the consultation process. The proposed decisions are made based on the information available at the time, and the PMRA will consider the comments and information received during consultation using a science-based approach before making a final decision. The final decision will be published on the Pesticides and Pest Management portion of Health Canada's website and it will include a summary of the comments received during the consultation and PMRA's responses to the comments.

The registration status of products and conditions of use of pesticide products on the market are not impacted by proposed re-evaluation or special review decisions. This may be the case only when final decisions are made. However, at any point during the re-evaluation or special review of a pesticide, the *Pest Control Products Act* allows the PMRA to cancel or amend the registration of registered pest control products, if there are reasonable grounds to believe this is necessary to deal with a situation that endangers human health or safety or the environment.

Proposed Re-evaluation Decision for Cypermethrin

After a re-evaluation of the insecticide cypermethrin, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of products containing cypermethrin for sale and use in Canada.

An evaluation of available scientific information found that products containing cypermethrin do not present unacceptable risks to human health or the environment when used according to the proposed label directions. As a requirement of the continued registration of cypermethrin, new risk reduction measures are proposed for the end-use products registered in Canada.

This proposal affects the end-use products containing cypermethrin registered in Canada. Once the final re-evaluation decision is made, the registrants will be instructed how to address any new requirements.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for cypermethrin and presents the reasons for the proposed re-evaluation decision. It also proposes new risk reduction measures to further protect human health and the environment.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the assessment of cypermethrin.

The PMRA will accept written comments on this proposal up to 90 days from the date of publication of this document. Please forward all comments to Publications (please see contact information indicated on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

The PMRA's pesticide re-evaluation program considers potential risks, as well as value, of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2012-02, *Re-evaluation Program Cyclical Re-evaluation*, presents the details of the current re-evaluation approach.

What is Cypermethrin?

Cypermethrin is a synthetic pyrethroid insecticide used to control a broad range of pests on a wide variety of sites including forestry, greenhouse food crops, industrial oilseed crops, livestock for food, terrestrial feed crops, terrestrial food crops, outdoor ornamentals and for non-agricultural industrial pest management. It is applied by farmers, farm workers and professional applicators using conventional aerial equipment (rotary and fixed wing aircraft) and conventional ground equipment such as boom sprayers, airblast sprayers, mist blowers and hand held sprayers.

Health Considerations

Can Approved Uses of Cypermethrin Affect Human Health?

Products containing cypermethrin are unlikely to affect your health when used according to the proposed label directions.

Potential exposure to cypermethrin may occur through the diet (food and drinking water), when handling and applying products containing cypermethrin or during contact with treated surfaces. When assessing health risks, two key factors are considered: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed. The health effects noted in animals occur at doses which are much higher than levels to which humans are normally exposed when pesticide products are used according to label directions. Due to the similarity of structure, mode of action and toxicological findings as well as the inability to analytically distinguish between stereoisomers, the human health risk assessment for cypermethrin was based on data for cypermethrin and zeta-cypermethrin.

In laboratory animals, the acute oral toxicity of cypermethrin ranges from low to high. Cypermethrin is of low acute inhalation and dermal toxicity. Cypermethrin is a slight eye and skin irritant. Exposure to cypermethrin is not expected to cause an allergic skin reaction; however, itching, tingling or burning sensations of the skin may occur.

Registrant-supplied short- and long-term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of cypermethrin to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment included effects on the nervous system and on body weight. Some potential concern for increased sensitivity of the young exposed to cypermethrin was noted. Longer-term dosing with cypermethrin resulted in lung tumors in female mice and a slight increase in testicular tumors in male rats.

The risk assessment protects against the above noted effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occur in animal tests.

Residues in Food and Water

Dietary risks from food and water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose (ARfD) or chronic reference dose (acceptable daily intake or ADI). An ADI is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Cypermethrin belongs to a family of pyrethroids which is comprised of cypermethrin, alpha-cypermethrin and zeta-cypermethrin. These three chemicals are mixtures of the same isomers and, consequently, their uses result in human exposure to the same isomers. Analytical methods for current residue monitoring do not differentiate the cypermethrins. Therefore, the dietary risk assessments were conducted by combining the uses of the three chemicals; that is, the exposure estimates represent exposures to all three cypermethrins, from crops or commodities treated with any one of them (including imports), and from drinking water. Acute (probabilistic) and chronic dietary exposures were conducted for different population subgroups including children and women of reproductive age. A cancer risk assessment was conducted for the general population.

The acute dietary exposure (from food and drinking water) estimate for the general population, at the 99.9th percentile, represented 24% of the ARfD. Acute exposure estimates for population subgroups ranged from 17% of the ARfD (females 13-49 years of age) to 70% of the ARfD (all infants less than 1 year of age). The chronic exposure estimate for the general population was less than 1% of the ADI. Chronic exposure estimates for population subgroups ranged from less than 1% to 3% of the ADI; the most exposed population subgroup was children 1-2 years of age. The dietary cancer risk for the general population was approximately 1×10^{-6}. Thus, acute, chronic and cancer dietary risks from exposure to all cypermethrins are not of concern.

The *Food and Drugs Act* prohibits the sale of adulterated food; that is, food containing a pesticide residue that exceeds the specified maximum residue limit (MRL). Pesticide MRLs are specified for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. An MRL represents the maximum amount of residues that may remain on food when a pesticide is used according to label directions, and serves as a food safety standard. The Canadian Food Inspection Agency is responsible for monitoring the Canadian food supply for pesticide residues and the determination of compliance with MRLs specified by Health Canada.

Canadian MRLs for cypermethrin are currently specified for a wide range of commodities. The complete list of specified MRLs can be found on the PMRA's MRL Database, an online query application that allows users to search for specified MRLs, regulated under the *Pest Control Products Act*, for pesticides or food commodities (http://pr-rp.hc-sc.gc.ca/mrl-lrm/index-eng.php). For all other agricultural commodities, including those registered for use in Canada but without a specific MRL, residues must not exceed the default MRL of 0.1 ppm as per subsection B.15.002(1) of the *Food and Drug Regulations*.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern when products containing cypermethrin are used according to the proposed label directions.

Residential applicator exposure is not expected, as domestic-class products containing cypermethrin are not registered in Canada.

Residential postapplication exposure may occur while performing activities on trees in residential areas treated with cypermethrin by a commercial applicator. Residential postapplication risk is not of concern.

Non-occupational scenarios were aggregated with dietary exposure (food and drinking water). The resulting aggregate risks are not of concern.

Occupational Risks

Occupational risks to handlers are not of concern when products containing cypermethrin are used according to the proposed label directions.

Risk estimates associated with mixing, loading and applying activities are not of concern when mitigation (additional personal protective equipment) is considered.

Postapplication risks are not of concern when products containing cypermethrin are used according to the proposed label directions.

Postapplication occupational risk assessments consider exposures to workers entering treated sites in agriculture and performing activities, such as scouting and hand harvesting. Postapplication risks to workers are not of concern, provided that the current restricted-entry intervals (REIs) are adhered to, and that some specific REIs are lengthened.

Environmental Considerations

What Happens When Cypermethrin Is Introduced Into the Environment?

Products containing cypermethrin are not expected to pose risks of concern to the environment when used according to proposed label directions.

When cypermethrin is released into the environment, it can enter soil and surface water. Cypermethrin is not expected to persist in soils because it is broken down fairly rapidly by microbes. Laboratory studies, field studies, computer modelling and groundwater monitoring all indicate that cypermethrin is unlikely to move downward through the soil and enter groundwater. When cypermethrin enters aquatic environments, it rapidly moves from water into sediments where it is broken down by microbes and is not expected to persist. Cypermethrin is detected very infrequently at levels that would result in risk to aquatic organisms in available Canadian surface monitoring data.

Cypermethrin can vaporize and enter the atmosphere, but is unlikely to persist or move in air to remote locations such as the Arctic. Cypermethrin is not expected to accumulate in the tissues of organisms.

Cypermethrin may pose risks to pollinators, beneficial insects, and aquatic organisms when they are exposed to high enough conncentrations. For pollinators, potential risks are mitigated by restricting application to periods when bees are not actively foraging. The potential risks to aquatic organisms are mitigated with spray buffer zones and recommendations to reduce run-off from fields. Toxicity statements are proposed on product labels for pollinators, beneficial insects and aquatic organisms.

Value Considerations

What is the Value of Cypermethrin?

Cypermethrin is of value for pest management in Canadian agriculture.

As a synthetic pyrethroid insecticide, cypermethrin is an Insecticide Resistance Action Committee (IRAC) Mode of Action (MoA) group 3 insecticide. It is of value as a very effective insecticide for a variety of uses and for rotation with the carbamates and organophosphates (MoA group 1A and 1B insecticides respectively) to delay the development of insecticide resistance.

For some of the registered uses of cypermethrin, there are few alternative active ingredients. The majority of the alternative active ingredients to cypermethrin are carbamates, organophosphates, or other synthetic pyrethroid insecticides. Several uses of cypermethrin have particular value for pest management due to the limited availability of alternative active ingredients, or for resistance management. Cypermethrin has been identified as a priority for pest management by growers and many of its uses were registered through the Minor Use program which is based on grower priorities.

Proposed Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. Following these directions is required by law. As a result of the re-evaluation of cypermethrin, the PMRA is proposing further risk-reduction measures in addition to those already identified on cypermethrin product labels. The additional risk-reduction measures are presented below.

Human Health

To protect mixer/loader/applicators, the following statements are proposed to be added to all agricultural product labels:

- Wear long-sleeved shirt, long pants and chemical-resistant gloves during mixing, loading, application, clean up and repair. In addition, wear goggles or face shield during mixing and loading.
- For mechanically pressurized handgun (MPHG) application to strawberry: Wear coveralls (over single layer of clothes) and chemical-resistant gloves during mixing, loading and application.

To protect workers entering treated sites, modified restricted-entry intervals (REI) are proposed to be added to all agricultural labels.

To protect bystanders, the following statement is proposed to be added to all commercial class product labels:

- Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

Tthe following statement is proposed to be added to all agricultural product labels:

- Crop Rotation: Rotational crops may not be planted within 30 days after the last application, except crops on which cypermethrin is registered (listed on this label).

Environment

- Environmental hazard statements for bees, beneficial insects, and aquatic organisms are proposed.
- Spray buffer zones for non-target aquatic habitat will be required. The PMRA is in the process of revising its approach to buffer zones for all chemicals. The current buffer zones may be modified when the new approach has been finalized. Updated buffer zones will be identified in the regulatory decision document.
- A label statement advising that the application of cypermethrin should be restricted to periods when pollinators are not actively foraging is proposed.
- To reduce the potential for run off of cypermethrin to adjacent aquatic habitats, precautionary statements for sites with characteristics that may be conducive to run-off and when heavy rain is forecasted are proposed. In addition, a vegetative strip between the treatment area and the edge of a water body is proposed to reduce run-off of cypermethrin to aquatic areas.

Next Steps

Before making a final re-evaluation decision on cypermethrin, the PMRA will consider all comments received from the public in response to this consultation document. A science-based approach will be applied in making a final decision on cypermethrin. The PMRA will then publish a Re-evaluation Decision[2] that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

[2] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Science Evaluation

1.0 Introduction

Cypermethrin is a non-systemic broad spectrum, Insecticide Resistance Action Committee (IRAC) 3 insecticide, which disrupts the function of neurons by interaction with the sodium channel prolonging sodium permeability. Sodium channels are involved in the propagation of action potentials along nerve axons. Cypermethrin has good residual activity on treated plants. It works by contact, stomach and anti-feeding action.

Following the re-evaluation announcement for cypermethrin, BASF Canada Inc. and United Phosphorous Inc., the technical registrants and primary data providers in Canada, indicated continued support for all uses included on the label of commercial class end-use products.

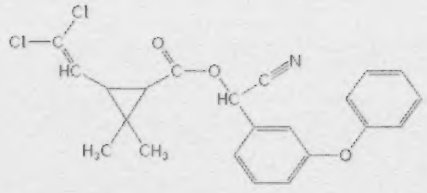
2.0 The Active Substance, its Properties and Uses

2.1 The Technical Grade Active Ingredient, Its Properties and Uses

2.2 Identity of the Technical Grade Active Ingredient

Common name		Cypermethrin
Function		Insecticide
Chemical Family		Pyrethroid
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	(Ξ)-cyano(3-phenoxyphenyl)methyl (1Ξ,3Ξ)-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-1-carboxylate
2	**Chemical Abstracts Service (CAS)**	cyano(3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
CAS Registry Number		52315-07-8
Molecular Formula		$C_{22}H_{19}Cl_2NO_3$

Structural Formula



Molecular Weight 416.3

Registration Number	Purity of the Technical Grade Active Ingredient (%)
19186	95.0
28092	97.78
32074	97.2

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.3 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 25°C	2.0×10^{-4} mPa
Ultraviolet (UV) / visible spectrum	pH λ_{max} (nm) 7 216 0.91 219 11.31 224
Solubility in water at 20°C	0.004 mg/L (pH 7)
n-Octanol/water partition coefficient	Log K_{ow} = 6.6
Dissociation constant	Not applicable, no dissociation expected

2.4 Description of Registered Cypermethrin Uses

Appendix I lists all cypermethrin products that are registered under the authority of the *Pest Control Products Act*. All uses were supported by the registrant at the time of re-evaluation initiation and were therefore considered in the health and environmental risk assessments of cypermethrin.

Uses of cypermethrin belong to the following use-site categories: forestry, greenhouse food crops, industrial oilseed crops, livestock for food, terrestrial feed crops, terrestrial food crops, non-agricultural, industrial and residential pest management for non-food sites and ornamental outdoors. Products containing cypermethrin are applied by farmers, farm workers and professional applicators using conventional aerial equipment (rotary and fixed wing aircraft) and

conventional ground equipment such as boom sprayers, airblast sprayers, mist blowers and hand held sprayers.

3.0 Impact on Human and Animal Health

Toxicology studies in laboratory animals describe potential health effects resulting from various levels of exposure to a chemical and identify dose levels where no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species.

3.1 Toxicology Summary

A summary of the toxicity profile and endpoints for the health risk assessment of cypermethrin is found in Appendix II.

Cypermethrin is a synthetic pyrethroid insecticide, and is referred to as a Type II pyrethroid due to the presence of an α-cyano group. It is a racemic mixture of 8 stereoisomers (four diasterioisomeric pairs) resulting from differing conformations at 3 chiral centers. Zeta-cypermethrin is composed of the same 8 stereoisomers, but is enriched with isomers containing the S-conformation at the cyano-bearing chiral carbon (~90% in zeta-cypermethrin; 50% in cypermethrin). Due to the similarity of structure, mode of action and qualitative toxicological findings, the human health risk assessment for cypermethrin has been based on data for cypermethrin and zeta-cypermethrin. This approach is further justified by the fact that analytical methods for current residue monitoring cannot distinguish between cypermethrin stereoisomers. An extensive toxicology database is available for the assessment of human health risks of cypermethrin and zeta-cypermethrin, including numerous papers in the scientific literature. The scientific quality of the available data is considered to be high. It is recognized that alpha-cypermethrin is used in regulatory jurisdictions outside of Canada. As no petition for registration or import MRL has been received by the PMRA at this time for alpha-cypermethrin, no toxicology data have been received for assessment of this moiety. In the event that a submission for registration or import MRL is received, reference values for the cypermethrin family may have to be re-visited.

Synthetic pyrethroids induce neurotoxic effects primarily by binding to voltage-dependant sodium channels in neurons thereby delaying the closing of sodium channels and causing the depolarization of neurons. This affects action potentials and results in either repetitive activity (Type I pyrethroids) or blockage of nerve conduction (Type II pyrethroids). Type II pyrethroids such as cypermethrin typically induce the "CS syndrome" which is characterized by choreoathetosis (involuntary excessive movements progressing to sinuous writhing), sedation, salivation, dyspnoea, clonic seizures and tremors. Impairment of motor activity and acoustic startle response are also characteristic of Type II pyrethroids.

Available toxicokinetic data for cypermethrin are based on radiolabel studies in which rats were administered either 1) cypermethrin (a racemic mixture of cis- and trans-cypermethrin isomers), 2) cis-cypermethrin isomers only or 3) trans-cypermethrin isomers only. In rats treated orally

with a single low dose of cypermethrin, absorption from the gastrointestinal tract was rapid and extensive, with blood concentrations reaching peak levels within three hours in both sexes.

Administration of a single low oral dose of either cis- or trans-cypermethrin also resulted in rapid elimination in both sexes, with 90% of the administered dose eliminated within 48 hours. Elimination occurred primarily in urine and to a lesser extent via feces, with significant biliary contribution. Elimination in exhaled air was negligible.

Twenty-four hours following administration of a single low oral dose of cypermethrin in rats, the highest tissue residues were detected in fat, followed by skin, intestine, liver and kidney; levels in brain were low. Levels of radioactivity in most tissues decreased rapidly, with half-lives ranging from approximately five to nine hours, though extended half-lives were noted in fat (>24 hours) and skin (13 hours). Residue levels in fat were up to 3.7-fold higher in females, compared to males, three days following administration of a single low oral dose. Eight days following administration, levels in fat did not decrease substantially; low levels persisted in organs associated with the metabolism and elimination of cypermethrin (kidney and liver) likely due to the slow release of cypermethrin from fat.

Absorption was slower and less extensive following administration of a single high-dose, compared to a single low oral dose. Peak plasma levels were achieved between 8-hours (in females) and 23-hours (in males), with a greater proportion of the administered dose eliminated in feces. Seven days post-dosing, the highest levels were detected in fat, skin, intestine, liver and kidney with low levels of radioactivity detected in brain tissue. Levels of radioactivity in fat one week after dosing were proportionately greater in rats receiving a single high oral dose of cypermethrin, compared to animals receiving a single low oral dose.

Following repeated exposure in rats to a low oral dose of cypermethrin for up to 70 days, peak levels of radioactivity were noted in most tissues by treatment day 56. Levels of radioactivity decreased rapidly in most tissues following cessation of exposure, reaching background levels within 15 days. However, low levels of cypermethrin remained in fat and skin 50 days following the last exposure. At termination, the relative proportions of cis- and trans-isomers in fat were approximately 88% and 12%, respectively. The elimination of cypermethrin from adipose tissue was biphasic due to the initial rapid elimination of trans-cypermethrin, followed by the slower elimination of cis-isomer; reported elimination half-lives in fat were 18 days for cis-isomer and 3-days for trans-isomer.

Based on the results of a rat developmental neurotoxicity study conducted with zeta-cypermethrin, cypermethrin is assumed to distribute to the developing fetus via placental transfer, and to the neonate via maternal milk. While concentrations in maternal milk were proportional to maternal intake, levels in fetal plasma were slightly lower than maternal plasma and did not correlate with maternal dietary levels, suggesting limited placental transfer.

Cypermethrin is metabolized in the liver of rats, with similar metabolic profiles noted in males and females. Metabolism occurs principally by ester cleavage yielding the cyclopropanecarboxylic acid and 3-phenoxybenzyl moiety. The 3-phenoxybenzyl moiety is eliminated in urine as the sulphate conjugate of 3-(4'-hydroxyphenoxy) benzoic acid) and 3-phenoxybenzoic acid, and the cyclopropanecarboxylic acid is transformed primarily to the ester

glucuronide prior to elimination. Unchanged cypermethrin was the major compound recovered in feces. Other minor fecal metabolites identified in rats were 3-phenoxybenzoic acid, 3-(4-hydroxyphenoxy)benzoic acid, 4-hydroxy-cis-cypermethrin and trans-hydroxy-cis-cypermethrin.

Acute oral toxicity studies in rodents conducted with cypermethrin or zeta-cypermethrin indicated a range of low to high acute toxicity depending on the vehicle used. Clinical signs of toxicity following oral exposure were characteristic of disruption of the autonomic nervous system and indicative of the "CS syndrome" including salivation, excessive grooming, motor incoordination, tremors, choreoathetosis, pawing and burrowing. No significant sex-related differences in toxicity were noted. Age-related sensitivity was apparent in two oral comparative lethality studies conducted in rats with cypermethrin, with greater sensitivity noted in pups and weanlings, compared to adults, based on LD_{50} values. In acute dermal studies, cypermethrin was of low acute toxicity in rats and rabbits, but induced clinical signs of neurotoxicity in both species at high doses. Cypermethrin caused low acute inhalation toxicity in rats and slight ocular and dermal irritation in rabbits. Cypermethrin was not a dermal sensitizer in guinea-pigs in a supplemental assay conducted by the Buehler method.

Based on repeat-dose guideline studies conducted by the oral route, the most sensitive indicators of toxicity were signs of neurotoxicity (tremors, irregular gait, incoordination, hypersensitivity to noise, disorientation in dogs) and body weight effects, with mortality and more severe neurotoxic signs (ataxia, clonic convulsions, splayed hindlimbs, walking on toes, extreme irregularities in gait, heavy breathing and chewing of extremities) noted in rodents and dogs at higher oral doses. In these studies, the dog was most sensitive species, followed by the rat, mouse and rabbit. There was a slight durational effect with regard to toxicity in dogs, but not rodents, based on the observation of tremors and mortality at lower doses in dogs in longer-term oral studies. Other notable effects at higher oral doses in repeat-dose studies included liver effects in rats and mice, haematological and renal effects in rats and testicular effects in all species tested. No sex-related differences in sensitivity were noted, despite the greater deposition of cypermethrin in the adipose tissue of female rats in toxicokinetic studies, compared to males.

Consistent with oral studies, signs of neurotoxicity were also noted in rats following short-term nose-only inhalation exposure to cypermethrin. Reduced body weight and excessive salivation were the critical effects at the lowest concentrations, with haematological effects, decreased activity, reduced stability, tip toe gait, head/paw flicking and tail erection noted at higher inhalation concentrations.

There was no indication of systemic toxicity in rats following short-term dermal exposure to zeta-cypermethrin at the limit dose, though dermal irritation was evident at the lowest dose tested. No systemic or dermal irritative effects were observed in non-abraded rabbits treated with cypermethrin in polyethylene glycol, though similar treatment of abraded skin of rabbits resulted in systemic and dermal toxicity. Toxicokinetic data suggest that highly lipophilic cypermethrin may be sequestered in the skin and slowly released into the systemic circulation.

In neurotoxicity studies and standard repeat-dose toxicity studies, exposure to cypermethrin or zeta-cypermethrin induced toxicological effects in all species (rodents, dogs, hens) which were consistent with Type II pyrethroids, including mortality, decreased body weight, salivation, tremors, decreased motor activity, splayed/dragging hindlimbs, severely impaired gait,

hypersensitivity, chewing, tremors and convulsions. Throughout the database, cypermethrin induced signs of local paraesthesia (chewing of extremities, burrowing, pawing, excessive grooming) as an acute effect distinct from irritation.

In acute neurotoxicity studies, the time of peak effect varied from 1.5-hours post-dosing in Long-Evans rats, to 4-hours in Sprague-Dawley rats. Microscopic neuropathology in the sciatic nerve (including axonal breaks, myelin degeneration, swelling and vacuolation) was seen in several rat studies conducted with cypermethrin, but only at high dose levels.

There was evidence of more severe neurological effects in the young, compared to adults, in a developmental neurotoxicity (DNT) study in rats treated with zeta-cypermethrin and range-finding DNT studies in rats conducted with cypermethrin and zeta-cypermethrin. In the DNT study conducted with zeta-cypermethrin, offspring had reduced body weights, impaired learning and memory, alterations in brain morphometrics and effects on functional observational battery (FOB) parameters, in the presence of reduced maternal body weight only. In the range-finding DNT studies, changes in brain morphometrics (cypermethrin) and decreased motor activity (zeta-cypermethrin) were noted in offspring, in the absence of maternal effects. Severe offspring toxicity in the form of decreased pup viability, decreased body weight, delayed physical development and altered FOB parameters in the presence of reduced maternal body weight was recorded in a non-guideline DNT study conducted in mice treated orally with cypermethrin prior to mating only.

In general, pyrethroid neurotoxicity is correlated with peak concentrations of the parent compound in blood, with bolus dosing resulting in larger internal doses and greater toxicity, compared to dietary administration. As the design of the DNT study does not consider the time of peak effect and may miss the window of peak toxicity for the pyrethroids, neurobehavioural assessments of the young in the DNT study may not be particularly informative. It is known that the metabolic clearance of pyrethroids in rats increases during maturation, primarily due to increased hepatic enzyme activity. Incomplete maturation of enzyme systems in the liver which detoxify pyrethroids may result in increased pyrethroid concentrations in target tissues (brain) and increased susceptibility of the young to toxicity, compared to adults receiving the same oral dose. Given the limitations of the DNT study in this regard, an adequate comparison of the sensitivity of the young animal is currently not available. A comparative oral gavage neurotoxicity study conducted in pups, weanling and adults, which considers the time of peak effect, could address this uncertainty. In the interim, this uncertainty has been reflected in the form of a database uncertainty factor.

Zeta-cypermethrin was not genotoxic in a battery of in vitro and in vivo tests; however, studies with cypermethrin produced mixed results. In guideline in vitro studies, cypermethrin was negative in gene mutation assays and chromosome aberration and sister chromatid exchange assays in human lymphocytes and Chinese hamster bone marrow cells. Equivocal results were noted in a micronucleus assay with human lymphocytes. Cypermethrin was negative in a dominant lethal assay and an unscheduled DNA synthesis assay conducted in vivo. Positive results were obtained in Comet assays performed in vitro and in vivo. Additional positive results were obtained in non-guideline assays (DNA adducts) and in five supplemental studies assessing chromosome aberrations, sister chromatid exchange and micronuclei in Swiss mouse cell lines.

There was evidence of tumorigenicity with cypermethrin in mice and rats in long-term dietary assays. Cypermethrin increased the incidence of benign Leydig cell tumors in male rats. These tumors were considered to be treatment-related in view of consistent evidence of testicular toxicity and anti-androgenic activity of cypermethrin throughout the database. However, these tumours were only marginally increased and of low toxicological significance with respect to human health. Cypermethrin administration also increased the incidence of benign lung adenomas in high-dose female mice; there was no treatment-related increase in malignant lung tumours. Treatment-related lung adenomas have been noted in several studies conducted in female mice with permethrin, a structurally similar compound. Based on the weight of evidence, it was determined that cypermethrin potentially poses a tumorigenic hazard; as such, a quantitative cancer risk assessment was undertaken.

There was no evidence of adverse effects on mating performance or fertility in multi-generation oral reproductive toxicity studies in rats conducted with cypermethrin or zeta-cypermethrin although studies were lacking estrus cycle and sperm measurements. Effects in parental animals were similar to those in repeat-dose oral toxicity studies (mortality, clinical signs of neurotoxicity and decreased body weight) and were evident at levels which were similar to those noted in non-pregnant females. Parental males treated with cypermethrin, but not zeta-cypermethrin, exhibited testicular atrophy. Reproductive effects were restricted to total litter loss in high-dose dams treated with zeta-cypermethrin resulting in the absence of a sufficient number of animals for mating in the second generation. There was no evidence of sensitivity of the young in either assay, with critical effects in offspring (decreased body weight) observed in conjunction with maternal toxicity. At higher oral doses of zeta-cypermethrin, mortality, neurotoxic signs, gastrointestinal/urinary tract bleeding and small testes were also evident in offspring. Offspring mortality in this investigation commenced during early lactation and was most pronounced during late lactation, likely due to increased consumption of test diet. Reproductive toxicity was also reported in mice (reduced number of pregnant mice, reduced number of pups/litter and increased number of dead pups/litter) treated by gavage during mating, in a non-guideline DNT study.

Based on the Tier I weight-of-evidence evaluation of existing data by the United States Environmental Protection Agency (USEPA) Endocrine Disruptor Screening Program (USEPA, 2010a), cypermethrin has the potential to interact with the androgen hormone system. In literature studies, cypermethrin displayed anti-androgenic activity in in vitro androgen receptor binding assays using yeast reporter genes, an in vitro androgen receptor transcriptional activation assays and an in vivo Hershberger assay in rats. Cypermethrin was equivocal/weakly positive in an in vitro estrogen receptor competitive binding assay and positive using the pS2 gene expression assay. Treatment-related functional and morphological changes in the testes were consistently noted throughout the cypermethrin database. Reduced relative testes weights were reported following repeated oral exposure in rats, mice and dogs, and short-term dermal exposure to abraded skin of rabbits. There was testicular toxicity in parental rats and offspring receiving zeta-cypermethrin or cypermethrin in multi-generation reproductive toxicity studies. In specialized repeat-dose oral studies to assess male reproductive effects, histopathological changes in the testes, abnormal sperm morphology, decreased testicular and epididymal sperm counts, increased serum FSH and LH, decreased serum and testicular testosterone levels and decreased expression of androgen receptors and steroidogenic regulatory proteins were observed

in mice and rats treated with cypermethrin. Supplementary data in mice suggest that these testicular effects can be induced with in utero and lactational exposure into adulthood.

As full assessments of female reproductive function and male testicular health were not conducted in existing reproductive toxicity studies, and the current literature identifies anti-androgenic activity and functional and morphological changes in the testes, there exists some uncertainty regarding the point of departure for male and female reproductive effects. This uncertainty is addressed through the application of a database uncertainty factor until further data are submitted to clarify the point of departure.

In developmental toxicity studies, cypermethrin and zeta-cypermethrin did not result in developmental effects in rats or rabbits following gavage administration (in oil) of maternally-toxic doses. The most notable signs of toxicity in dams were mortality, clinical signs of neurotoxicity (ataxia, hypersensitivity, spasms, convulsions, splayed hind-limbs) and anorexia.

3.1.1 *Pest Control Products Act* Hazard Considerations

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to take into account the completeness of the data with respect to the exposure of, and toxicity to, infants and children as well as potential pre- and post-natal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicology database for the assessment of risk to infants and children, most of the required studies for risk assessment were available including oral developmental toxicity studies in rats and rabbits, multi-generation reproductive toxicity studies in rats and DNT studies in mice and rats. However, male (and possibly female) reproductive effects have not been adequately assessed based on evidence of anti-androgenic activity and testicular toxicity in experimental species at doses which are within the range of those selected for risk assessment purposes. This concern is addressed through the application of a database uncertainty factor.

With respect to concerns relevant to the assessment of risk to infants and children, there is no evidence of increased susceptibility in rats or rabbits to in-utero exposure in oral developmental toxicity studies, or increased susceptibility of the young in multi-generation reproductive toxicity studies in rats. However, there is residual uncertainty regarding the susceptibility of the young. Young animals have incomplete maturation of enzyme systems which detoxify pyrethroids and thus may be more susceptible due to higher and prolonged brain concentrations, compared to adults (Kim et al., 2010). In two acute oral comparative lethality studies conducted in rats, there was evidence of sensitivity of the young to the lethal effects of cypermethrin, compared to adults. Moreover, serious neurological effects were noted in offspring in a guideline DNT study conducted in rats with zeta-cypermethrin as characterized by impaired learning and memory, altered FOB parameters and morphometric changes in the brain at a dose which produced reduced maternal body weights only. Morphometric changes in the brain and decreased motor activity in offspring (in the absence of maternal toxicity) have also been reported in a supplemental DNT study conducted with cypermethrin in rats. Due to the lack of a comparative oral neurotoxicity study, an adequate assessment of sensitivity of the young is currently not

available and residual uncertainty remains concerning susceptibility of the young to potential neurotoxic effects. This concern was reflected through the use of a database uncertainty factor.

A 3-fold database uncertainty factor (UF_{DB}) was applied due to concerns of potential male reproductive effects, and/or for concerns regarding sensitivity of the young to neurotoxic effects for risk assessment purposes. Since these concerns were addressed with a database uncertainty factor, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Dietary Exposure and Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to cypermethrins from potentially treated imported foods is also included in the assessment. These dietary assessments are age specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when exposure exceeds 100% of the reference dose or the lifetime cancer risk estimate exceeds 1×10^{-6} (in other words, one-in-a-million). PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute, chronic and cancer risk assessment procedures.

Residue estimates used in the dietary risk assessment may be based conservatively (in other words, using upper bound estimates) on the maximum residue limits (MRLs) or the field trial data representing the residues that may remain on food after treatment at the maximum label rate. Surveillance data representative of the national food supply may also be used to derive a more accurate estimate of residues that may remain on food when it is purchased. These include the Canadian Food Inspection Agency (CFIA) National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program (USDA PDP). Specific and empirical processing factors as well as specific information regarding percent of crops treated may also be incorporated to the greatest extent possible.

Acute, chronic and cancer exposure and risk assessments for cypermethrins were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™; Version 4.02) program which incorporates food consumption data from the National Health and Nutrition Examination Survey/"What We Eat in America" (NHANES/WWEIA) dietary survey for the years 2005-2010 available through CDC's National Center for Health Statistics (NCHS). Cypermethrin belongs to a family of pyrethroids which is comprised of cypermethrin, alpha-cypermethrin and zeta-cypermethrin. These three chemicals are mixtures of the same isomers and, consequently, their uses result in human exposure to the same isomers. Analytical methods for current residue monitoring do not differentiate the cypermethrins. Therefore, the dietary risk assessments were conducted by combining the uses of the three chemicals; that is, the exposure estimates represent exposures to all three cypermethrins, from

crops or commodities treated with any one of them (including imports), and from drinking water. Only cypermethrin is currently registered in Canada; import MRLs have been established for zeta-cypermethrin. Alpha-cypermethrin is not registered in Canada and import MRLs have not been established; however, it is used in the US and other countries on commodities that can be imported into Canada.

The acute and chronic/cancer exposure estimates are considered to be highly refined (more precise) as monitoring residues, percent crop treated, experimental processing factors and domestic/import data were used to the extent possible. However, the assessments retained a certain level on conservatism due to the use of MRLs/tolerances or anticipated residues, (field trial residues) for a few commodities. None of these commodities was a major contributor to the total exposure to cypermethrins. For more information on dietary risk estimates or residue chemistry information used in the dietary exposure assessment, see Appendices III and IV.

3.2.1 Determination of Acute Reference Dose (ARfD)

General Population (including pregnant women, infants and children)

To estimate acute dietary risk, the $BMDL_{20}$ (benchmark dose 95% lower confidence limit at the 20% effect level) of 5.2 mg/kg bw from an acute oral neurotoxicity study conducted with cypermethrin was selected, based on reduced motor activity in adult rats (PMRA#2007554). Reduced motor activity was considered the critical endpoint since it is a sensitive neurobehavioral endpoint which is relevant to pyrethroid toxicity and is derived by a relevant route and duration of exposure. The $BMDL_{20}$ was specifically selected based on the reported variability of motor activity in control rats in the literature (Crofton *et al.*, 1991). Since there is concern that the critical endpoint in adults may not be ideal for assessment of the young, a 3-fold database uncertainty factor (UF_{DB}) was applied for risk assessment purposes. Consequently, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Considerations section. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were also applied, resulting in a composite assessment factor (CAF) of 300.

$$\text{ARfD} = \frac{\text{BMDL}_{20}}{\text{CAF}} = \frac{5.2 \text{ mg/kg bw}}{300} = 0.02 \text{ mg/kg bw}$$

3.2.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk (from food and drinking water) was calculated considering the highest ingestion of cypermethrin that would be likely on any one day, and using food and water consumption, and food and water residue values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, the acute dietary exposure is not of concern.

The acute probabilistic risk assessment was conducted using available CFIA and PDP monitoring data. The USEPA Standard Operating Procedure (SOP) 99.3 was used for crop translations when necessary. MRLs/tolerances were used for a few commodities for which no

monitoring data were available. In addition, the following inputs were used: available percentage of crops treated (PCT) information in Canada and in the US; 100% crop treated for commodities for which no PCT information was available; available information on domestic production and import supply; and available experimental processing factors. Dietary exposure evaluation model (DEEM) default processing factors were used when experimental processing factors were not available. Drinking water contribution to the exposure was accounted for by direct incorporation of the estimated environmental concentration (EEC), obtained from water modelling (see Section 3.3), into the DEEM.

The acute dietary exposure estimate for the general population, at the 99.9th percentile, represents 24% of the ARfD. Exposure estimates for population subgroups range from 17% of the ARfD (females 13-49 years of age) to 70% of the ARfD (all infants less than 1 year of age). Drinking water contribution to the acute exposure is very low, accounting for less than 4% of total exposure for the most exposed population subgroup. Acute dietary exposure is, therefore, not of concern.

3.2.3 Determination of Acceptable Daily Intake (ADI)

General Population (including pregnant women, infants and children)

To estimate dietary risk from repeated exposure, a no observed adverse effects level (NOAEL) of 5.0 mg/kg bw/day was selected based on the results of the following co-critical toxicity studies: the oral NOAEL values of 5.0/5.7 mg/kg bw/day in dogs treated with cypermethrin for 12 months, the NOAEL of 5 mg/kg bw/day in the dietary subchronic neurotoxicity study in rats with zeta-cypermethrin, the NOAEL of 5.0 mg/kg bw/day in the oral DNT study in mice conducted with cypermethrin, the NOAEL of 7.3 mg/kg bw/day in the 2-year dietary rat study conducted with cypermethrin and the NOAEL of 9.0 mg/kg bw/day in the rat DNT study conducted with zeta-cypermethrin. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. Residual uncertainty regarding potential susceptibility of the young and inadequate assessment of testicular toxicity was addressed with a 3-fold UF_{DB}. Consequently, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Considerations section. Therefore, the composite assessment factor (CAF) is 300.

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{5.0 \text{ mg/kg bw/day}}{300} = 0.02 \text{ mg/kg bw/day}$$

The ADI provides a margin of 1250 to the lowest observed adverse effect level (LOAEL)(25 mg/kg bw/day) for testicular effects in acceptable repeat-dose oral toxicity studies, whereas the effect levels in supplemental repeat-dose oral toxicity studies were within the range of the NOAEL used for risk assessment purposes.

3.2.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk (from food and drinking water) was calculated using the average consumption of different foods and water, and the average residue values on those foods and

water. This estimated exposure to cypermethrins was then compared to the ADI. When the estimated exposure is less than the ADI, the chronic dietary exposure is not of concern.

The chronic assessment was conducted using average residues from the same CFIA and PDP monitoring data used in the acute assessment, adjusted with percent crop treated data and domestic/import statistics; anticipated residues (from field trials) for imported commodities for which no monitoring data were available; MRLs/tolerances for commodities for which no monitoring data or anticipated residues were available; experimental processing factors when available (otherwise DEEM default processing factors were used); and the chronic drinking water EEC point estimate obtained from modelling (see Section 3.3).

The chronic exposure estimate for the general population is less than 1% of the ADI. Chronic exposure estimates for population subgroups range from less than 1% to 3% of the ADI; the most exposed population subgroup is children 1-2 years of age. Chronic dietary exposure is, therefore, not of concern.

3.2.5 Cancer Assessment

Cypermethrin poses a potential tumorigenic hazard in humans based on assessment of the weight of evidence of carcinogenicity. There is evidence of tumorigenicity in mice and rats in-vivo and some evidence of genotoxicity. A cancer potency factor of 8.09×10^{-3} mg/kg bw/day^{-1} was derived based on lung adenomas in female mice treated with cypermethrin. Benign Leydig cell tumors in rats treated with cypermethrin were considered to be treatment-related but of low toxicological concern to human health.

3.2.6 Cancer Dietary Exposure and Risk Assessment

A dietary (food + drinking water) cancer risk assessment was conducted for the general population by using the same chronic residues as described in Section 3.2.4 and the drinking water EEC point estimate of 0.000059 ppm from Section 3.3.1. The estimated chronic exposure was then compared to the cancer potency factor (q_1*). A lifetime cancer risk that is equal or below 1×10^{-6} (one-in-a million) usually does not indicate a risk of concern for the general population when exposure occurs through pesticide residues in or on food, or to otherwise unintentionally exposed persons. Based on the q_1* approach, the lifetime cancer risk estimate from dietary exposure is approximately 1×10^{-6} and is, therefore, not of concern.

3.3 Exposure from Drinking Water

Residues of cypermethrins in potential drinking water sources were estimated from modelling.

3.3.1 Concentrations in Drinking Water

Estimated environmental concentrations (EECs) of cypermethrin in potential drinking water sources (groundwater and surface water) were generated using computer simulation models: the PRZMGW model for groundwater and the PRZM/EXAMS model for surface water (see Section 4.0 of this document for details). Cypermethrin concentrations in surface water were estimated in one type of vulnerable drinking water source, a small reservoir. Only EECs in surface water were considered, as concentrations in groundwater were practically zero. The Level 2 (refined) surface

water modelling was conducted for three different use rates reflecting those specified for the treatment of apples, strawberries and potatoes.
The highest yearly peak concentration of 0.0011 ppm from the potato scenario was used in the acute exposure assessment. The highest yearly average concentration of 0.000059 ppm was used in chronic (non-cancer) and cancer exposure assessments.

3.3.2 Drinking Water Exposure and Risk Assessment

Drinking water exposure estimates were combined with food exposure estimates, with EEC point estimates incorporated directly in the dietary (food + drinking water) assessments. Please refer to Sections 3.2.2 and 3.2.4.

3.4 Occupational and Non-Occupational Exposure and Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a margin of exposure (MOE). This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

3.4.1 Toxicology Endpoint Selection for Occupational and Non-Occupational Risk Assessment

Dermal Exposure

For short-, intermediate- and long-term dermal risk assessment in all populations, a NOAEL of 5.0 mg/kg bw/day was selected based on the offspring and parental NOAEL of 5.0 mg/kg bw/day cypermethrin in the DNT study in mice, and the offspring and parental NOAEL of 9.0 mg/kg bw/day zeta-cypermethrin in the rat DNT study. Decreased number of pups and litters, decreased number of live pups, increased number of dead pups, decreased body weight, delayed development and altered FOB parameters were noted in mouse pups receiving cypermethrin at the LOAEL, in the presence of maternal toxicity during treatment (pre-mating) and mating. Decreased body weight, altered FOB parameters, impaired learning and memory and changes in brain morphometrics were noted in rat pups receiving zeta-cypermethrin at the LOAEL, in the presence of maternal toxicity. The 21-day dermal toxicity study conducted with cypermethrin was not considered relevant for risk assessment purposes since it did not address the endpoints of concern. A target Margin of Exposure (MOE) of 300 was derived for the critical endpoint. This includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and a 3-fold UF_{DB} for concerns related to sensitivity of the young and potential testicular effects. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Considerations Section.

Inhalation Exposure

The most appropriate study for short-, intermediate- and long-term inhalation risk assessment in all populations is the short-term (nose-only) inhalation toxicity study in rats in which a NOAEL

of 2.7 mg/kg bw/day (0.01 mg/L) for cypermethrin was derived based on reduced body weight and excessive salivation at the LOAEL. This NOAEL was selected as it is based on an appropriate route of exposure and is protective of other systemic and neurological effects. A target MOE of 300 was selected, which includes 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and a 3-fold UF_{DB} for concerns related to sensitivity of the young and potential testicular effects. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Considerations Section.

Non-Dietary Incidental Oral Ingestion

For assessment of short- and intermediate-term non-dietary (incidental) oral exposure, a NOAEL of 5.0 mg/kg bw/day was selected based on the offspring and parental NOAEL of 5 mg/kg bw/day cypermethrin in the DNT study in mice, and the offspring and parental NOAEL of 9.0 mg/kg bw/day zeta-cypermethrin in the rat DNT study. This NOAEL was considered most relevant since it is based on sensitive endpoints in an appropriate population exposed by a relevant route and duration of exposure. Decreased number of pups and litters, decreased number of live pups, increased number of dead pups, decreased body weight, delayed development and altered FOB parameters were noted in mouse pups receiving cypermethrin at the LOAEL, in the presence of maternal toxicity during treatment (pre-mating) and mating. Decreased body weight, altered FOB parameters, impaired learning and memory and changes in brain morphometrics were noted in rat pups receiving zeta-cypermethrin at the LOAEL, in the presence of maternal toxicity. A target MOE of 300 was selected which includes 10-fold for interspecies extrapolation, 10-fold for intraspecies variability and a 3-fold UF_{DB} for concerns related to sensitivity of the young and potential testicular effects. The *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Considerations Section.

Cancer Assessment

A cancer potency factor of 8.09×10^{-3} mg/kg bw/day^{-1} was derived based on lung adenomas in female mice treated with cypermethrin. See section 3.2.5.

Dermal Absorption

A dermal absorption value of 7% was used for cypermethrin based on a weight-of-evidence approach which included consideration of a human in vivo study (Woolen *et al.*, 1992), other published studies (Capt *et al.*, 2007; Scott and Ramsey, 1987), physical-chemical properties and the dermal absorption of a structurally similar compound, permethrin.

3.4.2 Occupational Exposure and Risk Assessment

Workers can be exposed to cypermethrin through mixing, loading, or applying the pesticide, and when entering a treated site to conduct activities, such as scouting and hand harvesting.

Mixer, Loader, and Applicator Exposure and Risk Assessment

There are potential exposures to mixers, loaders, and applicators (M/L/A). The following scenarios were assessed:

- Mixing/loading of liquids;
- Applying liquids by open cab airblast to orchards (apple, nectarine, peach, pear, and plum) and grapes;
- Applying liquids by open cab groundboom to all crops, except orchards, grapes and greenhouse tobacco seedlings;
- Aerial application of liquids to canola, potatoes, sunflowers and corn (sweet and field).
- Applying liquids with a right-of-way sprayer to roadsides;
- Mixing/loading and applying with mechanically pressurized handgun (MPHG) to conifer seedlings (nursery), stevia and strawberries;
- Mixing/loading and applying with manually pressurized handwand (MPHW) to conifer seedlings (nursery), stevia and strawberries;
- Mixing/loading and applying with backpack equipment to stevia and strawberries; and
- Applying ear tags to beef and dairy cattle.

Based on the number of applications and the timing of application, workers applying cypermethrin would generally have a short-term exposure. Custom applicators may have a short- to intermediate-term exposure. Short- to intermediate-term exposure was assumed for application to greenhouse tobacco seedlings since this crop is seasonal in greenhouses.

Mixer/loader and applicator (M/L/A) exposure was estimated based on the following personal protective equipment (PPE):

- Baseline PPE: long pants, long-sleeved shirts and chemical-resistant gloves (unless otherwise specified). For groundboom application, this scenario does not include gloves, as the data quality was better for non-gloved scenarios than gloved scenarios.
- Mid-Level PPE: cotton coveralls over long pants, long-sleeved shirts and chemical-resistant gloves.

No appropriate chemical-specific handler exposure data were available for cypermethrin. Therefore, dermal and inhalation exposures were estimated using data from the *Pesticide Handlers Exposure Database* (PHED), *Version 1.1* and the Agricultural Handler Exposure Task Force (AHETF).

The PHED is a compilation of generic M/L/A passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of PPE. In most cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing coveralls. This was estimated by incorporating a 75% clothing protection factor for coveralls, where applicable. Inhalation exposures were based on light inhalation rates (17 L/min) except for backpack applicator scenarios, which were based on moderate inhalation rates (27 L/min).

The unit exposures for the open cab airblast scenario were derived from the appropriate AHETF study. Inhalation unit exposures are based on light inhalation rates (17 L/min) unless otherwise stated.

Mixer, loader and applicator exposure estimates are based on the best available data at this time.

For commercial application of ear tags to cattle, measured exposure data are not available and existing database models are not appropriate to estimate worker exposure during handling (application and removal) of ear tags. Herd treatment is anticipated; however, considering the low frequency of application, design of the product as a slow release of cypermethrin over time and the current label requirement to wear chemical-resistant gloves during application or when otherwise handling the tag, potential worker exposure is not expected to be of concern.

Calculated dermal and inhalation MOEs for mixer/loaders and applicators of cypermethrin exceeded target MOEs for all uses, and therefore are not of concern, provided that mid-level PPE is worn when treating strawberries with mechanically-pressurized handgun equipment.

Cancer risk estimates for mixer/loaders and applicators of cypermethrin were less than 1×10^{-5}, and therefore are not of concern.

The mixer/loader and applicator assessment is outlined in Appendix V, Tables 1-2.

Postapplication Worker Exposure and Risk Assessment

The postapplication occupational risk assessment considered exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact, such as scouting and hand harvesting.

Based on the cypermethrin use pattern, there is potential for short- to intermediate-term postapplication exposure to cypermethrin residues for workers.

Activity specific transfer coefficients (TC) from the Agricultural Re-entry Task Force (ARTF) were used to estimate postapplication exposure resulting from contact with treated foliage at various times after application. Dislodgeable foliar residue (DFR) refers to the amount of residue that can be dislodged or transferred from a surface, such as the the leaves of a plant. A TC is a factor that relates worker exposure to dislodgeable residues. TCs are specific to a given crop and activity combination (for example, hand harvesting apples, scouting late season corn) and reflect standard clothing worn by adult workers. Postapplication exposure activities include (but are not limited to): scouting, weeding, hand-harvesting and transplanting. For more information about estimating worker postapplication exposure, refer to PMRA's Regulatory Proposal PRO2014-02, *Updated Agricultural Transfer Coefficients for Assessing Occupational Postapplication Exposure to Pesticides*.

There were no chemical-specific DFR studies submitted to the PMRA for the re-evaluation of cypermethrin. Therefore, the following defaults were used:

- A default peak DFR value of 25% of the application rate was used for all crops; and
- A dissipation rate of 10% per day was assumed for all crops, except greenhouse tobacco seedlings.

PMRA's Science Policy Note SPN2014-02, *Estimating Dislodgeable Foliar Residues and Turf Transferable Residues in Occupational and Residential Postapplication Assessments*, presents further details on the derivation and use of these defaults for pesticide assessments.

For workers entering a treated site, restricted entry intervals (REIs) are calculated to determine the minimum length of time required before they can safely enter after application. An REI is the period of time that must elapse before residues decline to a level where performance of a specific activity results in acceptable exposures (greater than the target MOE).

Although there is potential dermal exposure to workers handling treated livestock following ear-tag application, these exposures are expected to be low.

The PMRA is primarily concerned with the potential for dermal exposure for workers performing postapplication activities in crops treated with a foliar spray. Based on the vapour pressure of cypermethrin, inhalation exposure is not likely to be of concern, including in greenhouses, provided that the minimum 12-hour REI is followed.

For most scenarios, calculated dermal MOEs for worker postapplication exposure to cypermethrin in agricultural crops exceeded the target MOE at the minimum 12-hour REI, and therefore are not of concern.

Calculated dermal MOEs for workers harvesting corn and girdling and turning grapes reached the target MOE at an REI of five days and seven days, respectively (see Appendix V, Table 3). These REIs are considered agronomically feasible.

For the REIs required for the non-cancer assessment, the cancer risk estimates are less than 1×10^{-5} for all postapplication activities, and therefore are not of concern.

3.4.3 Non-Occupational Exposure and Risk Assessment

Non-occupational risk assessment involves estimating risks to the general population, including youth and children, during or after pesticide application.

The USEPA has generated standard default assumptions for developing residential exposure assessments for both applicator and postapplication exposures when chemical- and/or site-specific field data are limited. The assumptions and algorithms may be used in the absence of, or as a supplement to, chemical- and/or site-specific data and generally result in high-end estimates of exposure. The assumptions and algorithms relevant to the cypermethrin re-evaluation are outlined in the Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessments 2012 under "Section 4: Gardens and Trees".

Residential Handler Exposure and Risk Assessment

A residential applicator refers to an adult who uses or applies a domestic-class product in or around the home. Domestic-class products containing cypermethrin are not registered in Canada. Therefore, a residential applicator assessment is not required.

Residential Postapplication Exposure and Risk Assessment

Residential postapplication exposure refers to an exposure scenario in which an individual is exposed through dermal, inhalation, and/or incidental oral (non-dietary ingestion) routes as a result of activities occurring in a residential environment that has been previously treated with a pesticide. For cypermethrin, the area could have been treated by a commercial applicator hired to treat trees in a residential area.

There is potential for short-term exposure to adults, youths (11 to <16 years old), and children (6 to <11 years old) through contact with transferable residues following applications of cypermethrin to trees. It is assumed that younger children (< 6 years old) will not engage in the types of activities associated with these areas (for example, pruning and harvesting fruits) to the same extent as older children or adults. Apple trees were chosen as the representative crop (maximum application rate, maximum number of applications per year). For the residential postapplication assessment, transfer coefficients were derived from the US Residential SOPs 2012 for activities conducted on trees, such as pruning.

Postapplication inhalation exposure was considered to be negligible due to low vapour pressure and expected dilution in outdoor air.

Calculated MOEs for dermal residential postapplication exposure to cypermethrin exceeded the target MOE and are not of concern. The cancer risk estimates were less than 1×10^{-6}, and therefore are not of concern.

The residential postapplication risk assessment is outlined in Appendix V, Tables 4-5.

3.5 Aggregate Exposure and Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

3.5.1 Toxicology Endpoint Selection for Aggregate Risk Assessment

For aggregate risk assessment of the general population (including pregnant women, infants and children) for any duration, the selected toxicological endpoints are clinical signs and decreased body weight. For oral exposure, the NOAEL values and assessment factors are the same as those identified for the ADI (see section 3.2.3). For inhalation aggregate risk assessment, the NOAEL values and assessment factors are the same as those identified for the inhalation risk assessment (see section 3.4.1). With regards to the dermal route, there were no adverse systemic effects noted following repeated dermal dosing. However, it was considered appropriate to give consideration to the endpoints that were selected for the route-specific dermal assessment, namely, the developmental effects (including pup body weight reductions) observed in the oral DNT studies. These developmental effects were elicited at a dose level (10 or 21 mg/kg bw/day orally) that also produced clinical signs and/or body weight changes in maternal adult animals.

No clinical signs and/or body weight changes were observed in adult animals in the dermal studies up to the limit dose of 1000 mg/kg bw/day. For these reasons, it was considered overly conservative to aggregate the endpoints from the oral DNT studies in the risk assessment and it was not appropriate to include the dermal route in the aggregate risk assessment.

An aggregate risk assessment is required for the cancer endpoint since it is assumed that this endpoint is relevant to all routes of exposure (that is, oral, dermal and inhalation).

3.5.2 Residential, Non-Occupational, and Dietary Aggregate Exposure and Risk Assessment

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures.

For the aggregate non-cancer risk assessment, inhalation exposures are not expected and dermal exposures were not included as explained in section 3.5.1. Therefore, the aggregate non-cancer assessment would be limited to dietary exposures only (see section 3.2.6)

For the cancer aggregate assessment for cypermethrin, the following scenario has the potential of co-occurrence:

- Lifetime postapplication cancer dermal exposure from residential trees + chronic dietary (food + drinking water).

The aggregate lifetime cancer risk estimates were 1×10^{-6} or less (1×10^{-7}) and therefore are not of concern (Appendix V, Table 6). Dietary exposure was the major contributor to exposure, with very low contribution from residential exposure.

3.5.3 Human Biological Monitoring Data

Human biomonitoring (HBM) data from the Canadian Health Measures Survey (CHMS; cycles 1 & 2; 2007-2011) and the Maternal-Infant Research on Environmental Chemicals-Child Development Plus (MIREC-CD Plus; 2013-2014[3]) were considered in the cypermethrin re-evaluation. Pyrethroid metabolites were included in the suite of compounds measured. The exposure estimates for cypermethrin were determined based on the levels of cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (cis-DCCA) and trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (trans-DCCA). This is a conservative (upper bound) assumption since it assumes all these metabolites come from cypermethrin, although the metabolites are common to other registered pyrethroids (cyfluthrin and permethrin).

In addition to the biomonitoring data, five human pharmacokinetic studies were available for cypermethrin (Eadsforth and Baldwin, 1983; Eadsforth *et al.*, 1988; Woollen *et al.*, 1992; Ratelle *et al.*, 2015; Cote *et al.*, 2014) and were used to determine the amount of cis and trans-DCCA metabolites excreted following administration of the parent compound, cypermethrin.

[3] Unpublished data from the Population Studies Division, Healthy Environments and Consumer Safety Branch, Health Canada (received December 2014).

Equations for estimating daily urinary creatinine excretion were used to calculate daily exposure estimates. As such, urinary excretion fraction values of 46% and 74% were selected for cis- and trans-DCCA, respectively. For the non-cancer risk assessment, it was assumed that all DCCA metabolites would have the same urinary excretion fraction as cis-DCCA (conservative assumption). For the cancer risk assessment, urinary excretion fraction of 66% was used. This was determined by multiplying the urinary excretion fraction of each isomer with its relative urinary concentration as measured in the CHMS and MIREC-CD Plus biomonitoring studies. The CHMS and MIREC-CD Plus metabolite data were normalized by each individual's body weight and extrapolated to a full day value using daily creatinine excretion values (determined for each individual based on their height and weight) based on the equations from Mage *et al.* (2008).

Based on the human biological monitoring data, the non-cancer risk estimates exceeded the target MOE (Appendix V, Table 7) and the cancer risk estimates were 1×10^{-6} (Appendix V, Table 8), and therefore are not of concern. These results support the aggregate risk assessment conducted for cypermethrin using the PMRA's standard methodology for assessing risks from pesticides.

3.6 Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Cypermethrin belongs to a group of insecticides commonly known as the pyrethroids. Pyrethroids and pyrethrins have a common mechanism of toxicity wherein they all possess the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. Upon completion of the re-evaluation of the individual chemicals in the pyrethroid group, it will be determined whether a cumulative effects assessment is necessary and if so, this will be performed with all relevant chemicals of the common mechanism group.

Currently, work is underway by a consortium of pyrethroid registrants to develop data to help address issues of comparative sensitivity of young and adult animals to synthetic pyrethroid neurotoxicity. The PMRA will review this information when it becomes available.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Cypermethrin enters the terrestrial environment when it is used as an insecticide on a variety of grain, cereal, fruit and vegetable crops as well as well as on conifer, tobacco and corn seedlings and on roadside summer fallow. Cypermethrin is expected to be slightly to moderately persistent in aerobic soil (time taken to decline to 50% of the original concentration (DT50)= 20-61 days). The major transformation products are CO_2 and a mixture of cis- and trans-dichlorovinyl acid (DCVA). Minor transformation products include 3-phenoxybenzoic acid (3-PBA). Under anaerobic soil conditions, cypermethrin is expected to be moderately persistent (DT50 53-63 days). The major transformation products are a mixture of cis- and trans-DCVA, 3-PBA and CO_2.

Cypermethrin is considered to be non-volatile under field conditions from the reported vapour pressure (2.5×10^{-9} mm Hg). The Henry's Law constant (3.4 × 10-7 $atm.m^3.mol^{-1}$), and 1/H value of 2.8×10^5, indicate that cypermethrin is, however, slightly volatile from water and moist soil surfaces.

Cypermethrin is practically immobile in soil due to its strong adsorption onto soil particles and its insolubility in water. The cypermethrin transformation products 3-PBA and trans-DCVA, however, have a high potential for mobility in soil as they are weakly sorbed. When taking into consideration the criteria of Cohen et al. (1984) and the groundwater ubiquity score (GUS), it was determined that cypermethrin is unlikely to leach to groundwater. This conclusion is also supported from soil column leaching experiments and computer modelling and field studies which all indicate that cypermethrin residues are not expected to leach into groundwater.

Cypermethrin can enter the aquatic environment through spray drift and run-off from the application site. Hydrolysis is an important route of transformation under alkaline conditions but cypermethrin is increasingly stable towards neutral and acidic conditions. Phototransformation is not expected to contribute to the dissipation of cypermethrin from the water layer in the photic zone.

In aquatic environments, cypermethrin is expected to be non-persistent to moderately persistent (aerobic whole system DT50 = 7 days; anaerobic whole system DT50 = 6.7-181 days) and partition into sediment. Three major transformation products were identified under aerobic conditions as 3-phenoxybenzoic acid (3-PBA), trans-dichlorovinyl acid (trans-DCVA) and cis-dichlorovinyl acid (cis-DCVA), with one minor transformation product identified as dichlorovinyl acid-dicarboxylic acid (DCVA-di-COOH). Two major transformation products were identified under anaerobic conditions as 3-phenoxybenzoic acid (3-PBA) and trans-dichlorovinyl acid (trans-DCVA). Sediments are shown to be an important sink for cypermethrin residues. As a result, exposure to cypermethrin of organisms living in the water column is expected to be short lived.

The octanol/water partition coefficient (log Kow) was reported to be 6.54, which indicates that cypermethrin has a high potential for bioaccumulation in biota. Steady-state bioconcentration factors (BCFs) for whole fish range from 3.5 – 1200 wet weight. Bioconcentration factors for chironomid larvae exposed to cypermethrin in water and sediment range from 34 - 385 (whole body). The depuration half-life for cypermethrin in chironomids (23 hours) and fish (eight days) indicates that residues of cypermethrin in biota are rapidly cleared. Bioaccumulation in biota, is therefore not expected to be a concern.

Environmental fate data for cypermethrin and its transformation products, in the terrestrial and aquatic environment, are summarized in Table 1 and 2 of Appendix VI, respectively.

4.2 Environmental Risk Characterization

The environmental risk assessment determines the potential for adverse ecological effects in each environmental compartment by comparing the ratio of the estimated environmental exposure to the ecotoxicological effect. The estimated environmental concentration (EEC) is the initial or cumulative concentration of pesticide in the various sources of food, water and soil to which the

organism is exposed. EECs are calculated by different methods for each media (food, water or soil). If multiple applications of pesticide are used, cumulative EECs are determined by using the DT50 using the minimum time interval between applications for each environmental media.

The risk assessment is initially conducted using a screening-level scenario which assumes maximum exposure (EEC) and the most sensitive toxicological endpoint for the organism of interest. This assumes direct application or over spray to the environmental media (food, water, soil) to which the organism is exposed. This is the most conservative scenario and generally does not reflect the exposure to which an organism would be subject to when the pesticide is applied according to the label instructions. Risk to the environment is calculated as a risk quotient (RQ) which is the ratio between the environmental exposure and the toxicological endpoint for the organism (RQ = EEC/toxicological endpoint). For characterizing acute risk, acute toxicity values (for example, LC50, LD50, and EC50) are divided by an uncertainty factor. The uncertainty factor is used to account for differences in inter- and intra-species sensitivity as well as varying protection goals (for example, community, population, individual). Thus, the magnitude of the uncertainty factor depends on the group of organisms that are being evaluated (for example, 10 for fish, 2 for aquatic invertebrates). The difference in value of the uncertainty factors reflects, in part, the ability of certain organisms at a certain trophic level (feeding position in a food chain) to withstand, or recover from, a stressor at the level of the population. When assessing chronic risk, the no observed effect concentration (NOEC) or NOEL is used and an uncertainty factor is not applied.

RQ values greater than or equal to 1 (≥ 2 for beneficial arthropods, ≥ 0.4 for honeybees) are considered to equal or exceed the level of concern (LOC) which may result in potentially harmful effects to the organism. RQ values less than 1 (< 2 for beneficial arthropods, < 0.4 for honeybees) are not considered to be a concern to the organism because they are below the LOC. In the latter case, no further assessment is carried out. If the RQ is greater than or equal to 1, (≥ 2 for beneficial arthropods, ≥ 0.4 for honeybees) then a refinement of the risk assessment is done to assess the LOC using scenarios which are a better approximation of exposure or toxicological effects and less conservative. Refinements can include exposure from the fraction of pesticide which drifts onto non-target habitats, instead of assuming 100% over spray, and exposure from the amount of pesticide predicted in run-off, instead of assuming direct application to water (100% exposure). The refinements may also consider different toxicity endpoints or a percentile of a species sensitivity distribution rather than the most sensitive endpoint. They may also consider the results of a mesocosm study using several species rather than the toxicity from a single species. Further refinements to the risk assessment may consider the use of monitoring data collected in the field rather than EECs generated by a model.

4.2.1 Risks to Terrestrial Organisms

A summary of terrestrial toxicity data for cypermethrin is presented in Appendix VI, Table 3. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with cypermethrin. The terrestrial assessment took into account the range of agricultural application rates that are registered for cypermethrin, taking into consideration that there may be multiple applications of cypermethrin in a use season.

Terrestrial Invertebrates

Earthworms

Earthworms could be exposed to cypermethrin when this compound reaches the soil upon application. The EEC is therefore calculated based on a direct application to bare soil at the maximum cumulative application rate. The maximum cumulative application rate takes into account the maximum labelled application rate, the application interval and the dissipation of the compound between applications.

A summary of the screening level risk assessment for earthworms is shown in Table 4 (Appendix VI). The RQs for earthworms resulting from acute exposure to cypermethrin were less than one and did not exceed the LOC at the screening level based on the EEC in soil from the highest cumulative application rate for agricultural uses (apples – three airblast applications of 101.8 g a.i./ha with a 7 day interval). Cypermethrin is therefore not expected to pose an acute risk to earthworms.

Honey bees (*Apis mellifera*)

Foraging bees could be exposed directly to cypermethrin spray droplets during application or to cypermethrin residues found on the surface of leaves (contact exposure). Foraging bees could also be exposed to cypermethrin through the ingestion of pollen and nectar contaminated from direct spray. In addition, brood may be exposed to cypermethrin and its metabolites as foraging bees bring contaminated pollen and nectar back to the hive.

A tiered approach was used to assess the risk from these routes of exposure. For the screening level (Tier I) assessment, risk quotients were calculated for the contact and oral routes of exposure using toxicity data from laboratory studies. For the Tier II assessment, risk at the colony level was evaluated based on results from semi-field studies.

Tier I assessment

The single lowest application rate (28.5 g a.i./ha on sunflowers) was used as the contact exposure estimate from foliar applications. In order to compare the application rate to the acute contact toxicity endpoint derived in laboratory studies (µg a.i./bee), a conversion from kg a.i./ha to µg a.i./bee is required. The proposed upper-bound residue value for estimating exposures to honey bees is based on the maximum residue value reported by Koch and Weisser 1997 (2.4 µg a.i./bee per 1 kg a.i./ha). The estimated residues per bee following a single application of 28.5 g a.i./ha on sunflowers is 0.068 µg a.i./bee. A risk quotient was calculated by dividing this value by the 48-h contact LD50 value of 0.023 µg a.i./bee.

The oral exposure estimate for adult bees is calculated by multiplying the lowest single application rate (28.5 g a.i./ha on sunflowers) by 29 µg a.i./bee per kg/ha. This conversion is based on nectar consumption rates for forager bees primarily derived from Rortais et al. (2005) and Crailsheim et al. (1992 and 1993). Following the conversion, the estimated oral exposure is 0.827 µg a.i./bee based on the single application rates for sunflowers. A RQ was calculated by dividing this value by the 48-h oral LD50 value of 0.172 µg a.i./bee.

The LOC for the Tier 1 acute exposure is 0.4. This value is based on a median slope of 3.2 for the dose response curve from acute contact and oral toxicity studies and a limit of 10% mortality (amount of mortality test guidelines allowed in control groups). The risk quotients for acute contact and oral toxicity to honeybees exceed the level of concern at the lowest single application rate Table 4 (Appendix VI). Cypermethrin, therefore, is expected to pose a risk to honey bees at all application rates.

Tier II assessment

Because a potential for concern was identified during the screening level (Tier I) assessment, the risk was further characterized using results from studies carried out under more realistic use conditions. For the Tier II assessment, risk at the colony level was evaluated based on results from field studies.

Cypermethrin was applied to flowering oilseed rape (the first to winter-sown rape, the second to spring-sown rape) by helicopter, at a time when the crops were being actively foraged by bees from nearby colonies, thus representing a worst case exposure for the bees. The rate of application in both trials was 25 g a.i./ha. In the first trial on winter-sown rape, a large increase in bee mortality was noted following treatment with cypermethrin which decreased to levels in the control after three to four days. Cypermethrin did not have any lasting effects on hive populations of adult bees or brood areas. In the second trial on spring-sown rape, a large increase in bee mortality was found at the time of treatment which decreased to control levels after one to two days. Cypermethrin had a repellent effect (reduced foraging activity) on honey bees for up to 24 h after application. Following this period, foraging activity and pollen collection returned to levels observed in the control. Cypermethrin did not have any lasting effects on hive populations of adult bees or on brood areas.

Another field test was carried out on a 38-ha field of oilseed rape. The insecticide was sprayed on a central area of 13 ha during the morning at a rate of 50 g a.i./ha. High levels of mortality were recorded on the three days following treatment. The results also showed that the bees avoided visiting the flowers as soon as the treatment was made, especially during the first two days. From the third day after the treatment, the visits to the rape flowers increased, reaching control levels on the fifth day.

Honey bee brood and whole colonies were exposed to alpha-cypermethrin (an insecticidally active isomer of cypermethrin) by foliar application of the test material to full bloom lacy phacelia (*Phacelia tanacetifolia*) at a nominal rate of 30 g a.i./ha in 400 L water /ha. Results of the study indicate that alpha-cypermethrin applied at a rate of 30 g a.i./ha may result in significant effects on adult mortality and early bee brood development. Most of the adverse effects on honey bees observed were transient (mortality significantly elevated for one day following application but tailing off; and reduced foraging for two days after application but rebounding). However, the percentage of brood terminated before a successful hatch (65%) indicates that alpha-cypermethrin has the potential to be of chronic concern to colony health.

In another field study, honey bee brood and whole colonies were exposed to alpha-cypermethrin by foliar application of the test material to full bloom lacy phacelia at a nominal rate of 30 g a.i./ha in 400 L water/ha. Sample locations included a treatment plot (2000 m2) and a control

plot (2400 m^2). The exposure phase was concluded 28 days after application. Assessments of mortality, foraging activity (flight density), behaviour of the bees, pollen collection, colony assessments (food stores, brood status, and hive populations), hive weight, and strength of the colonies were conducted throughout pre- and postapplication. Results of the field study indicated that alpha-cypermethrin does not have a lasting effect on mortality or brood development; however, statistical analyses were not conducted and colony replicate data was not available for analysis.

It should be noted that the application rates used in all the field studies conducted on honey bees are lower than many of the registered application rates for products containing cypermethrin in Canada, therefore colony level effects for these products may be underestimated in these studies.

Based on the results of the risk assessment, use restrictions were included on the label to minimize the exposure to cypermethrin. To mitigate risks to adult bees, all applications must be made early in the morning or late in the evening when bees are not active. This restriction reduces the probability of having bees present on the field during application and allows time for foliar residues to reach less hazardous levels before the bees resume foraging activities. Furthermore, it is recommended to avoid application of cypermethrin products during the crop blooming period or when blooming weeds are present in the treatment area. Without applications during the crop blooming period or when blooming weeds are present, cypermethrin would not be directly sprayed on pollen and nectar, thus limiting exposure to adult bees as well as brood.

Beneficial arthropods

The risk to non-target arthropods was assessed using maximum cumulative in-field and off-field EECs on plant surfaces, calculated from a direct spray on a field. The in-field EECs on plant surfaces for the lowest registered application (one aerial application on sunflowers at 28.5 g a.i./ha) was used for this assessment. Off-field exposure would be due to spray drift. Based on the crops and type of equipment used, spray drift factors are applied to the in-field exposure values to obtain off-field exposure values. The maximum spray drift deposition at one meter downwind from the point of application is 26% of the application rate for aerial application with fine spray quality. The maximum deposition on non-target plants located one metre downwind from the point of application would therefore be 7.4 g a.i./ha for aerial application on sunflowers. The screening RQs for in-field and off-field exposure resulting from the proposed use of cypermethrin on sunflowers is presented in Table 4 (Appendix VI). The in-field and off-field RQs exceeded the LOC of 2 for *Aphidius rhopalosiphi* (aphid parasitoid) and *Typhlodromus pyri* (predatory mite).

The risk to non-target arthropods was refined to reflect more realistic exposure by applying foliar interception. The screening level exposure estimates are assuming deposition to a 2-dimensional structure. Therefore, the values can be corrected to take into account the 3-dimensional structure where a certain fraction is intercepted by the crop (for in-field exposure) or the off-field vegetation (for off-field exposure). For the in-field EEC, crop-specific foliar interception factors (Fint) proposed by Linders et al. (2000) are applied to the application rate. A factor of 0.9 was used for flowering/ripening sunflowers. For the off-field EEC, a vegetation distribution factor of 0.1 is applied to the application drift rate. This default value was estimated to be appropriate based on data presented at the ESCORT workshop (Candolfi et al., 2001).

The calculated refined RQs for non-target arthropods are shown in Table 5 (Appendix VI). The refined in-field RQs still exceed the LOC of 1 for *A. rhopalosiphi* and *T. pyri*. The refined off field RQs still exceed the LOC for *T. pyri* but not for *A. rhopalosiphi* based on the proposed lowest application on sunflowers. Cypermethrin, therefore, is expected to pose a risk at all application rates, therefore, precautionary label statements are proposed for beneficial arthropods.

Terrestrial Plants

No data is available to assess the risk to terrestrial vascular plants at this time. Given that the mode of action (effect on the nervous system bydisruption of action potential in neurons) does not apply to plants, adverse effects to terrestrial vascular plants are not anticipated. Cypermethrin has been registered for many years for pest control on a variety of plant species at a wide range of application rates; no incidents have been reported in the US or Canada indicating that cypermethrin use causes adverse effects to terrestrial vascular plants. Based on the weight of evidence, cypermethrin is not expected to pose a risk to terrestrial plants.

Birds and mammals

To assess the risk to birds and mammals, the concentration of cypermethrin on various food items is used to estimate the amount of pesticide in the diet, or estimated daily exposure (EDE). Exposure is dependent on the body weight (BW) of the organism and the amount and type of food consumed. In the screening level assessment, a set of generic body weights is used for birds (20, 100, 1000g) and small wild mammals (15, 35, 1000 g) to represent a range of bird and small wild mammal species. For each body weight, the food ingestion rate (FIR; equivalent to food consumption) is based on equations from Nagy (1987).

The screening level risk assessment is based on simple methods, conservative exposure scenarios, and sensitive toxicity endpoints. For this assessment, EDEs are based on EECs that were calculated with maximum residue concentrations from the nomogram. At the screening level, only one feeding guild for each category of bird and mammal weights is selected. The selected feeding guilds are relevant to each specific size of bird or mammal and based on the most conservative residue values (maximum residues determined in the Hoerger and Kenaga nomogram). A diet consisting of 100% plant material is not considered realistic for small and medium sized birds (20 and 100g) and small mammals (15 g) and, therefore, was not included in the determination of EDE. The most conservative exposure estimate for these categories of bird and mammal weights is associated with a diet comprised of 100% small insects.

For the birds and mammals screening level assessment, the most sensitive endpoints from acute and reproductive/developmental toxicity studies were chosen. The NOEC for the Bobwhite quail (*Colinus virginianus*) of > 50 mg a.i./kg diet was converted to a daily dose by multiplying the LD50 value by the (FIR/BW). The default value used for FIR was 18.9 g dry weight food/day and the default value for BW was 178 g. The daily dose was therefore > 5.3 mg a.i./kg bw/day which was used to calculate the risk quotients to determine the chronic risk to wild birds feeding on contaminated vegetation at the site of cypermethrin application. This value is conservative because it is a greater than (>) value and the true NOEC is unknown.

Screening level EDEs based on the highest seasonal application rate on apples (101.8 g a.i./ha × 3 at 7-day interval applied by airblast) and RQ calculations for the active ingredient cypermethrin for birds and mammals showed the LOC is not exceeded for birds for the acute endpoints but is exceeded for reproductive effects (RQs <1.5 – <1.9) ; cypermethrin, therefore, is not expected to pose an acute risk to birds but could possibly result in reproductive effects. For mammals, the LOC for acute and reproductive effects is not exceeded for small wild mammals but is exceeded for 35 and 1000g mammals (RQs 1.1-3.1). Cypermethrin, therefore, could pose both an acute and reproductive risk to medium (35 g) and large sized (1000 g) mammals.

Given the conservative assumption made in the screening level, an additional assessment was conducted to further characterize the reproductive risk to birds and the acute and reproductive risk to medium- and large-sized mammals. The additional risk assessment used the mean residue values for calculating EECs and EDEs instead of the upper bound residue values used in the screening level risk assessment. The reproduction EDEs were calculated for each bird size and feeding preference item and the acute and reproduction EDEs were calculated for medium- and large-sized mammals for each feeding preference at the highest cumulative crop application rate (apples 101.8 g a.i./ha × 3 at 7-day intervals). The cumulative application rate was based on a default half-life of 10 days for foliar dissipation. This value is based on the foliar dissipation of a variety of active ingredients reported by Willis and McDowell (1987); with 93% of the foliar dissipation half-life less than 10 days, this value is considered to be a reasonable conservative estimate of typical foliar half-lives. The risk associated with the consumption of food items contaminated from spray drift off the treated field was assessed taking into consideration the spray drift spray quality of ASAE fine for airblast early season applications (74%) at 1 m downwind from the site of application.

The results of the expanded screening level risk assessment for birds is presented in Table 6 (Appendix VI). The off-field reproduction LOC for small and medium sized insectivores using maximum residues from small insects was exceeded by factors of 1.4 and 1.1 respectively. The off-field reproduction LOC for large sized herbivores using maximum residues from short grass and forage crops was exceeded by factors of 1.1 and 1.2 respectively. The only on-field reproduction LOC that was exceeded (by a factor of 1.1) using mean residues was for small insectivores.

The on-field assessment assumes that birds are being exposed to residues on food items at levels equivalent to those present immediately after application, that these levels remain constant over time and that birds would feed exclusively on a single food item (for example, small insects) within the treated area. In cases where risk quotients exceed the LOC, an additional analysis was conducted to determine the amount of contaminated food, expressed as a percentage of the daily diet that must be consumed in order to reach the LOC (calculated as 1/RQ × 100).

Given the conservative nature of this assessment, an acute and/or reproductive risk to birds both on-field and off-field is considered unlikely because the LOCs were only slightly exceeded for a few feeding guilds and birds would need to consume an unrealistically large proportion of a single contaminated food item over an extended time period (> 52% of their diet on-field and > 70% of their diet off-field using maximum residues and > 93% of their diet on-field using mean residues) to reach the LOC. In addition, the NOEC used in the assessment was a greater than (>) value (the true NOEC is unknown) which is conservative.

The results of the expanded screening level risk assessment for wild mammals are presented in Table 7 (Appendix VI). The off-field acute LOC for medium sized herbivores using maximum residues from short grass and forage crops was exceeded by factors of 1.6 and 1.4 respectively. The off-field reproduction LOC for medium sized herbivores using maximum residues from short grass, long grass and forage crops was exceeded by factors of 2.3, 1.4 and 2.1 respectively. The off-field reproduction LOC for large sized herbivores using maximum residues from short grass, and forage crops was exceeded by factors of 1.2 and 1.1 respectively. The only on-field LOC that was exceeded using mean residues was reproduction (by a factor of 1.1) for medium sized herbivores feeding on short grass.

Similar to the bird risk assessment, given the conservative nature of this assessment, an acute or reproductive risk to medium and large sized wild mammals both on-field and off-field is considered unlikely because the LOCs were either not exceeded or only slightly exceeded for many of the feeding guilds. Additionally, they would need to consume an unrealistically large proportion of a single contaminated food item over an extended time period (> 32% of their diet on-field and > 44% of their diet off-field using maximum residues and > 90% of their diet on-field using mean residues) to reach the LOC.

There are also uncertainties regarding the reproductive risk to medium- and large-sized herbivores. The chronic reproductive toxicity endpoint is a no effect concentration (two generation NOEL of 5.9 mg a.i./kg bw/day for the rat Rattus norvegicus). The lowest observed effect level (LOEL) was 43.4 mg a.i./kg bw/day where increased pup deaths were observed . The LOEL (at which effects actually occurred) is seven times greater than the NOEL value which was used for the risk assessment. The NOEL is therefore a very conservative value and reproductive effects from the use of cypermethrin may in fact, be of minimal concern. If the LOEL is used instead of the NOEL, the on-field reproduction RQs for medium-sized herbivores using maximum residues from short grass, long grass and forage crops were reduced from 3.1, 1.9 and 2.9 respectively to 0.4, 0.3, and 0.4 respectively. The on-field reproduction RQs for large-sized herbivores using maximum residues from short grass, long grass and forage crops was reduced from 1.7, 1.0 and 1.5 respectively to 0.2, 0.1 and 0.2 respectively. The LOC is, therefore, not exceeded using on-field maximum nomogram residues when the LOEL is used in the risk assessment.

4.2.2 Risks to Aquatic Organisms

A summary of aquatic toxicity data for cypermethrin is presented in Table 3 (Appendix VI).

Screening Level Assessment

The initial aquatic assessment conducted is a deterministic screening level risk assessment. This approach is conservative, and primarily designed to identify the taxonomic groups which are not at risk and/or the use scenarios which do not pose risks of concern. The initial conservative screening level EEC calculations for aquatic systems were based on a direct application to water depths of 15 and 80 cm following a single application at 28.5 g a.i./ha on sunflowers which is the lowest registered application rate in Canada. The 15 cm depth was chosen to represent a temporary body of water that could be inhabited by amphibians. The 80 cm depth was chosen to represent a typical permanent water body for applications of pest control products in agriculture.

Multiple acute toxicity endpoints were available for freshwater invertebrates, freshwater fish and estuarine/marine invertebrates Table 3 (Appendix VI). The program ETX 2.0 was used to generate species sensitivity distributions (SSDs) for freshwater invertebrates and fish and estuarine/marine invertebrates based on normally distributed toxicity data. The hazardous concentration to 5% of the species (HC5) was then calculated for freshwater invertebrates, freshwater fish and estuarine/marine invertebrates from their respective SSD's. The HC5 values reported in Table 3 (Appendix VI) were used to calculate the risk quotients for these groups of taxa instead of the most sensitive species tested. This provides a more scientific endpoint that incorporates all of the data.

The LOC is exceeded for all freshwater and estuarine/marine taxa (RQs <6-10,000) with the exception of freshwater and estuarine/marine algae following a single application of 28.5 g a.i./ha on sunflowers. Since this is the lowest application rate registered in Canada, the LOCs resulting from all the remaining registered uses will be higher. The LOCs for freshwater and estuarine/marine algae following an application of 101.8 g a.i./ha × 3 on apples (the highest rate registered in Canada) were 0.44 and 1.3, respectively. The LOC of 1 was exceeded for estuarine/marine algae. A refined aquatic risk assessment, therefore, will be conducted on all taxa with the exception of freshwater algae.

Spray drift refinement

Similar to the terrestrial risk assessment, the risk to aquatic organisms from spray drift from the treated site was also assessed by taking into consideration drift deposition of spray quality of ASAE fine for ground boom (11%), airblast early season (74%) and aerial (26%) at 1 m downwind from the site of application. Table 8 (Appendix VI) summarizes the refined drift risk assessment of cypermethrin to aquatic organisms.

The LOC is exceeded for all of the freshwater and estuarine/marine taxa for all of the use-patterns and application methods with the exception of estuarine/marine algae. Spray buffer zones will, therefore, be proposed to mitigate the risk to aquatic organisms.

Runoff Refinement

For Level 1 aquatic ecoscenario assessment, EECs of cypermethrin from run-off into a receiving water body were simulated using the PRZM/EXAMS models. The PRZM/EXAMS models simulate pesticide run-off from a treated field into an adjacent water body and the fate of a pesticide within that water body. For the Level 1 assessment, the water body consists of a 1 ha wetland with an average depth of 0.8 m and a drainage area of 10 ha. A seasonal water body was also used to assess the risk to amphibians, as a risk was identified at the screening level. This water body is essentially a scaled down version of the permanent water body noted above, but having a water depth of 0.15 m.

The results of the assessment are summarized in Table 9 (Appendix VI). The maximum peak and 21-day EECs reported in Tables 11 and 12 (Appendix VI) were used for the acute and chronic risk assessments, respectively, for the application scenarios to apples, potatoes and sunflowers across the country. The acute LOCs are exceeded for freshwater invertebrates, fish and aquatic plants on potatoes and for amphibians on potatoes and sunflowers using the highest peak EECs

for many of the application scenarios. The chronic LOCs are exceeded for freshwater invertebrates and amphibians on potatoes. The acute and chronic LOCs for estuarine/marine taxa are exceeded, with the exception of algae, for all of the application scenarios. Aquatic organisms, therefore, may be at risk from cypermethrin residues in run-off following applications for the different use-patterns across the country. Standard label statements to mitigate run-off into aquatic habitats are therefore proposed on the label for all cypermethrin end-use products for agricultural uses.

Risk to aquatic organisms from concentrations of cypermethrin observed in surface water from Canadian monitoring data

An acute risk assessment was conducted on aquatic organisms using the maximum detected concentration (9.44 µg a.i./L) from surface water monitoring studies conducted in Canada. A chronic risk assessment was not conducted because chronic exposure is not expected to occur for cypermethrin in surface water. The results of the risk assessment are presented in Table 10 (Appendix VI).

The acute LOC is exceeded for both freshwater and estuarine/marine invertebrates and fish and for amphibians and aquatic plants, indicating that these organisms may be at risk from concentrations of cypermethrin in surface waters in Canada. The monitoring data were restricted to freshwater waterbodies so it is assumed that estuarine/marine surface waters would have similar concentrations of cypermethrin, however this is an uncertainty.

Another uncertainty regarding the acute risk assessment is that the duration of exposure to these concentrations is unknown, whereas the aquatic species used to generate the toxicity endpoints used in the analysis (including HC5's from SSDs) were exposed for a 96-hour period. If the actual exposure period at the monitoring sites was less than 96 hours, which is possible, then the calculated risk may be overestimated.

Cypermethrin was only detected in 8 out of 898 samples (0.9%) with a maximum concentration of 9.44 µg/L in Prince Edward Island. Five of these samples, collected in rivers, had levels exceeding the limit of solubility of 4 µg/L. According to the Pesticide Science Fund (PSF) reports, sampling in the Atlantic Region occurred mainly after rainfall events, so these concentrations probably resulted from run-off. It should be noted that the next highest concentration observed in surface water (0.38 µg a.i./L) is almost two orders of magnitude lower, so the 9.44 µg a.i./L observed in surface water from Prince Edward Island could be considered atypical for concentrations observed in surface waters across Canada (Appendix VII).

This analysis supports the previous spray drift and run-off refined risk assessments for freshwater and estuarine/marine taxa by showing that these actual concentrations observed in Canadian surface waters from monitoring data could present a risk to these organisms in some regions.

5.0 Value

Cypermethrin is of value for pest management in Canadian agriculture. As a synthetic pyrethroid insecticide, cypermethrin is an (IRAC) Mode of Action (MoA) group 3 insecticide. It is of value as a very effective insecticide for a variety of uses and for rotation with the carbamates and organophosphates (MoA group 1A and 1B insecticides respectively) to delay the development of insecticide resistance.

Most registered cypermethrin uses have value either as the sole active ingredient registered for use on the site to control the listed pest(s), or for resistance management. The majority of the alternative active ingredients to cypermethrin are carbamates, organophosphates, or other synthetic pyrethroid insecticides.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the Canadian Environmental Protection Act].

During the review process, cypermethrin and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-034 and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- Cypermethrin does not meet all Track 1 criteria, and is not considered a Track 1 substance. See Table 13 in Appendix VI for comparison with Track 1 criteria.
- Cypermethrin does not form any transformation products that meet all Track 1 criteria.

The use of cypermethrin is not expected to result in the entry of TSMP Track-1 substances into the environment.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical are compared against the list in the Canada Gazette. The list is used as described in the PMRA Notice of Intent NOI2005-015 and is based on existing policies and regulations including: DIR99-03; and DIR2006-026, and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the Canadian

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[4] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

[5] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

[6] DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

Environmental Protection Act (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Based on the manufacturing process used, impurities of human health or environmental concern as identified in the *Canada Gazette*, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in cypermethrin products.
- Technical grade cypermethrin does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[7].

7.0 Incident Reports

Since 26 April 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Incidents are classified into six major categories including effects on humans, effects on domestic animals and packaging failure. Incidents are further classified by severity, in the case of humans for instance, from minor effects such as skin rash, headache, etc., to major effects such as reproductive or developmental effects, life-threatening conditions or death.

The PMRA will examine incident reports and, where there are reasonable grounds to suggest that the health and environmental risks of the pesticide are no longer acceptable, appropriate measures will be taken, ranging from minor label changes to discontinuation of the product.

7.1 Human and Animal Incident Reports

As of 17 September 2015, there were seven human and 22 domestic animal incident reports in the PMRA database involving the active ingredient cypermethrin. There was a low degree of association between the reported effects and exposure to the pesticide in the human incidents, and some degree of association in the domestic animal incidents. In one human incident report, symptoms were consistent with effects reported in the literature. This incident occurred in Canada, and the subject experienced minor dermal symptoms following accidental contact with a contaminated glove. All but one of the domestic animal incidents occurred in the US; the Canadian incident was of minor severity. Domestic animals were exposed to a product containing cypermethrin, either via direct ingestion of the product or contact with the treated area.

These incident reports were considered in this evaluation. Overall, the findings do not impact the risk assessment.

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[7] DIR2006-02, *PMRA Formulants Policy*.

7.2 Environmental Incident Reports

Environmental incident reports are obtained from two main sources, the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the USEPA Ecological Incident Information System (EIIS). Specific information regarding the mandatory reporting system regulations that came into force 26 April 2007 under the *Pest Control Products Act* can be found at http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/index-eng.php.

As of 23 April 2014, there were two environmental incident reports in the PMRA database for cypermethrin. In the first report, a major environmental incident occurred following a fire in a chemical distribution warehouse. The douse water was released into a nearby creek and a large number of dead fish were subsequently observed in the creek. Several products were being stored in the warehouse at the time, including cypermethrin products. As cypermethrin was not one of the active ingredients detected in water samples, it was concluded that it was not associated with the fish mortality.

The second incident involved lobsters (exact number unknown) found dead in lobster traps off the coast of New Brunswick in November, 2009. Although it was unknown how the cypermethrin entered the environment, analysis of lobster tissue confirmed the presence of cypermethrin. Given the concentrations found in the lobster, it was considered probable that the active ingredient was a contributing factor in the lobster deaths.

Twenty-two incidents have been reported in EIIS in the United States for cypermethrin. The reported incidents have included lobsters, fish, crayfish, aquatic invertebrates, birds, mammals, and honey bees. Many of these incidents, however, were the result of misuse or off-label use of cypermethrin.

8.0 Organisation for Economic Co-operation and Development Status of Cypermethrin

Canada is part of the Organisation for Economic Co-operation and Development (OECD), which provides a forum in which governments can work together to share experiences and seek solutions to common problems.

As part of the re-evaluation of an active ingredient, the PMRA takes into consideration recent developments and new information on the status of an active ingredient in other jurisdictions, including OECD member countries. In particular, decisions by an OECD member to prohibit all uses of an active ingredient for health or environmental reasons are considered for relevance to the Canadian situation.

Cypermethrin is currently acceptable for use in other OECD member countries, including Australia, Europe and the United States. As of 18 March 2016, no decision by an OECD member country to prohibit all uses of cypermethrin for health or environmental reasons has been identified.

9.0 Proposed Re-Evaluation Decision

After a re-evaluation of the insecticide cypermethrin, Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing continued registration of cypermethrin and associated end-use products, provided that the risk reductionmeasures described in this document are implemented.

The proposed regulatory actions for cypermethrin are summarized in the following sections. The labels of Canadian end-use products are proposed to be amended to include the risk reduction measures listed in Appendix VIII.

9.1 Proposed Regulatory Actions

9.1.1 Proposed Regulatory Action Related to Human Health

The PMRA has determined that the dietary (food and drinking water), occupational and non-occupational risks are not of concern for all uses provided that the proposed mitigation measures are implemented. Details of the use pattern considered in the present risk assessment were partially based on additional information supplied by the registrant and/or other sources (for example, maximum number of applications and minimum interval between applications). This information and a 30 day plant back interval are proposed to be included on product labels, where applicable. All proposed label amendments are included in Appendix VIII.

9.1.2 Proposed Regulatory Action Related to Environment

To reduce the effects of cypermethrin in the environment, mitigation in the form of precautionary label statements and spray buffer zones will be required. Information that could facilitate buffer zone refinement may be submitted during the consultation period. The PMRA is in the process of revising its approach to buffer zones for all chemicals and will consult broadly on the revised approach prior to implementation. The buffer zone requirements proposed in this document are based on the PMRA's current approach. Buffer zones identified in this proposed decision document may be revised based on any new information received and on any future revisions to the Agency's approach to calculating buffer zones. Proposed environmental mitigation statements are listed in Appendix VIII.

9.2 Additional Data Requirements

No additional data are required.

List of Abbreviations

↑	Increased
↓	Decreased
µg	microgram(s)
♀	Females
♂	Males
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
AAFC	Agriculture and Agri-Food Canada
ADD	Absorbed Daily Dose
ADI	Acceptable daily intake
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APDM	Aminopyrine demethylase
ARfD	Acute reference dose
ARTF	Agricultural Re-entry Task Force
ASAE	American Society of Agricultural Engineers
AST	Aspartate aminotransferase
atm	atmosphere
ATPD	Area treated per day
BAF	Bioaccumulation Factor
BCF	Bioconcentration Factor
BMD	Benchmark dose
$BMDL_{20}$	Benchmark dose 95% lower confidence limit at the 20% effect level
BUN	Blood urea nitrogen
bw	Body weight
Bwg	Body weight gain
CAF	Composite assessment factor
CAS	chemical abstracts service
CF	Conversion factor
CHO	Chinese hamster ovary
cm	centimetres
cm^2	Square centimeter
CYM	Cypermethrin
d	day
DA	Dermal absorption
DFOP	double first order in parallel
DFR	Dislodgeable foliar residue
DMSO	Dimethyl sulfoxide
DNT	Developmental neurotoxicity

DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
dw	dry weight
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EDE	estimated daily exposure
EEC	estimated environmental exposure concentration
EIIS	Ecological Incident Information System
e-PRS	Electronic Pesticide Regulatory System
ER	Endoplasmic reticulum
F_0	Parental generation
F_1	First filial generation
F_2	Second filial generation
FC	food consumption
FIR	food ingestion rate
FOB	Functional observational battery
FSH	Follicle-stimulating hormone
g	gram
GD	Gestation day
GSH	Glutathione
GUS	Groundwater Ubiquity Score
h	hour
ha	hectare(s)
HB-EGF	Heparin-binding epidermal growth factor
HC5	hazardous concentration threshold for 5% of species
Hct	Hematocrit
HDL	High density lipoprotein
HDT	Highest dose tested
Hgb	Hemoglobin
HPLC	high performance liquid chromatography
IORE	Indeterminate Order Rate Equation Model
IRAC	Insecticide Resistance Action Committee
IUPAC	International Union of Pure and Applied Chemistry
Iv	Intravenous
K_d	soil-water partition coefficient
K_F	Freundlich adsorption coefficient
kg	kilogram
K_{oc}	organic-carbon partition coefficient

K_{ow}	octanol-water partition coefficient
L	litre
LADD	Lifetime Average Daily Dose
LC_{50}	lethal concentration 50%
LD	Lactation day
LD_{50}	lethal dose 50%
LDT	Lowest dose tested
LH	Luteinizing hormone
LMA	Locomotor activity
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOD	limit of detection
LOEC	lowest observed effect concentration
LOEL	lowest observed effect level
LOQ	limit of quantitation
m^2	Square meter
MC	Manufacturing Concentrate
MCH	Mean cell haemoglobin
MCV	Mean cell volume
mg	milligram
mL	millilitre
MoA	Mode of Action
MOE	Margin of Exposure
MPHG	Mechanically pressurized handgun
MPHW	Manually pressurized handwand
MS	mass spectrometry
N/A	not applicable
N/R	not required
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
nr	not reported
OC	organic carbon content
OM	organic matter content
PHED	Pesticides Handlers Exposure Database
PHI	Pre-Harvest Interval
pK_a	dissociation constant
PMC	Pest Management Centre
PMRA	Pest Management Regulatory Agency
PND	Post-natal day

PPE	Personal Protective Equipment
ppm	parts per million
PRZM/EXAMS	Pesticide Root Zone Model / Exposure Analysis Modelling System
PSF	Pesticide Science Fund
RBC	Red blood cells
REI	Restricted entry interval
RfD	Reference dose
RQ	risk quotient
RSD	relative standard deviation
S9	Mammalian metabolic activation system
SER	Smooth endoplasmic reticulum
SFO	Single first order
SSD	Species sensitivity distribution
StAR	Steroidogenic acute regulatory protein
Sub. No.	Submission number
$t_{1/2}$	half-life
TC	Transfer coefficient
TGAI	Technical Grade Active Ingredient
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
US	United States
UF_{DB}	Database uncertainty factor
URMULE	User Requested Minor Use Label Expansion
USEPA	United States Environmental Protection Agency
USC	Use Site Category
UV	ultraviolet
v/v	volume per volume dilution
WBC	White blood cell
Wt	Weight

Appendix I Products Containing Cypermethrin that are Registered in Canada as of 16 March 2016[1]

Registration Number	Marketing Class	Registrant Name	Product Name	Formulation Type	Net Contents	Guarantee
15738	Commercial	BASF Canada Inc.	RIPCORD 400EC AGRICULTURAL INSECTICIDE	Emulsifiable concentrate	1 L	Cypermethrin 407 g/L
24438	Commercial	Vétoquinol N.-A. Inc.	ELIMINATOR EAR TAGS	Slow release generator	10.5 g/tag; 10 tags per pouch	Cypermethrin 6%; Diazinon 11%
28795	Commercial	United Phosphorus Inc.	UP-CYDE 2.5 EC AGRICULTURAL	Emulsifiable concentrate	1 L, 3.79 L, 5 L and 10 L	Cypermethrin 250 g/L
30316	Commercial	Engage Agro Corporation	RIPCORD INSECTICIDE	Emulsifiable concentrate	1 L	Cypermethrin 407 g/L
30353	Manufacturing Concentrate	BASF Canada Inc.	RIPCORD 400 EC BULK INSECTICIDE	Emulsifiable concentrate	Bulk	Cypermethrin 407 g/L
19186	Technical Grade Active Ingredient	BASF Canada Inc.	CYPERMETHRIN TECHNICAL INSECTICIDE	Liquid	50 - 200 kg	Cypermethrin 95%
28092	Technical Grade Active Ingredient	United Phosphorus Inc.	CYPERMETHRIN TECHNICAL INSECTICIDE	Liquid	200 kg	Cypermethrin 97.78%
32074	Technical Grade Active Ingredient	Sharda CropChem Ltd.	SHARDA CYPERMETHRIN TECHNICAL INSECTICIDE	Liquid	25-200 kg	Cypermethrin 97.2%

[1]Excluding discontinued products or products with a submission for discontinuation.

Appendix II Toxicity Profile and Endpoints for Health Risk Assessment

Table 1 Toxicology Endpoints for Use in Health Risk Assessment for Cypermethrin

	RfD	Study NOAEL (or LOAEL)	CAF[1] or target MOE
Acute Dietary	ARfD = 0.02 mg/kg bw	$BMDL_{20}$ = 5.2 mg/kg bw acute oral neurotoxicity study with cypermethrin in rats (decreased motor activity)	300
Chronic Dietary	ADI = 0.02 mg/kg bw/day	NOAEL = 5.0 mg/kg bw/day <u>Co-critical studies:</u> 12 month dog study with cypermethrin, dietary subchronic neurotoxicity study in rats with zeta-cypermethrin, oral DNT study in mice with cypermethrin, 2-yr dietary rat study with cypermethrin, oral DNT study in rats with zeta-cypermethrin	300
Short-, Intermediate- and Long-Term Dermal[2]		NOAEL = 5.0 mg/kg bw/day <u>Co-critical studies:</u> oral DNT study in mice with cypermethrin, oral DNT study in rats with zeta-cypermethrin	300
Short-, Intermediate-and Long-Term Inhalation		NOAEL = 2.7 mg/kg bw/day 21-day inhalation toxicity study in rats (reduced body weight and excessive salivation)	300
Non Dietary Incidental Oral Ingestion		NOAEL = 5.0 mg/kg bw/day <u>Co-critical studies:</u> oral DNT study in mice with cypermethrin, oral DNT study in rats with zeta-cypermethrin	300
Aggregate Risk – Oral		NOAEL = 5.0 mg/kg bw/day <u>Co-critical studies:</u> 12 month dog study with cypermethrin, dietary subchronic neurotoxicity study in rats with zeta-cypermethrin, oral DNT study in mice with cypermethrin, 2-yr dietary rat study with cypermethrin, rat DNT study with zeta-cypermethrin	300
Aggregate Risk – Inhalation		NOAEL = 2.7 mg/kg bw/day 21-day inhalation toxicity study in rats (reduced body weight and excessive salivation)	300
Carcinogenicity	$Q^* = 8.09 \times 10^{-3}$ (mg/kg bw/day)$^{-1}$ based on lung adenomas in female mice treated with cypermethrin		

[1] CAF (Composite assessment factor) refers to the total uncertainty and *Pest Control Products Act* factors for dietary and residential risk assessment; MOE refers to the target margin of exposure for occupational assessment

[2] Since an oral NOAEL was selected, a dermal absorption factor of 7% was used in a route-to-route extrapolation.

Table 2 Toxicology Profile for Cypermethrin/Zeta-Cypermethrin

Note: Effects noted below are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight changes refer to both relative and absolute weights, unless otherwise indicated. Studies lacking a PMRA# utilized foreign study evaluations.

Study/Species	Results/Effects
Metabolism/Toxicokinetic Studies	
Absorption Distribution Metabolism Elimination – Gavage (Cypermethrin) Wistar Rats PMRA#1789426 PMRA#1789427 PMRA#1789428 PMRA#1789430 PMRA#1789432 PMRA#1789433 PMRA#1789434 PMRA#1789425 PMRA#1789435 PMRA#1789431	**Single High Dose/Single Low Dose** Absorption: With an acute low dose, absorption was rapid and extensive. Peak radioactivity levels in blood were noted 3-hours post-dosing; half-lives in blood ranged from 3 to 5 hours. Absorption was slower and less extensive following administration of a single high-dose. Peak plasma levels were noted after 8 to 23 hours, with a greater proportion of the parent compound eliminated in feces (46% to 59% of the administered dose). Distribution: Following acute exposure to low doses of cis-cypermethrin, tissue levels (both sexes) were highest in fat 24-hours (0.91-1.46 µg/g), 72-hours (0.83-1.04 µg/g) or 8 days (0.93-1.33 µg/g) following exposure. Levels of cis-cypermethrin in fat were up to 1.6-fold greater in females, compared to males, 24- and 72-hours post-exposure. After 8 days, levels in fat were similar in both sexes. After 42 days, the level of cis-cypermethrin in fat in ♀ rats was 0.05 µg/g (♂ not assessed). Levels of cis-isomer in brain tissue were low in both sexes. Tissue levels for trans-cypermethrin were generally lower than the corresponding values for cis-isomer, 72-hours post-dosing. The highest levels of radioactivity in both sexes were detected in fat (0.12-0.63 µg/g); levels in fat were up to 3.7-fold greater in females, compared to males, 72 hours after exposure. Levels of trans-cypermethrin in brain tissue were low in both sexes. Seven days following treatment with an acute high dose, radioactivity levels were highest in fat (13.6-21.3 µg/g), followed by skin, intestine, liver, kidney and ovaries; levels of radioactivity in the brain were low. Metabolism: Cypermethrin was rapidly metabolized in both sexes. The major metabolic pathway for cypermethrin is 1) arylhydroxylation at the para-position of the distal aromatic ring and 2) ester cleavage. Twenty-four hours post-dosing, the primary metabolites identified in urine were sulfate conjugates of 3-(4-hydroxyphenoxy) benzoic acid. Small amounts of 3-phenoxybenzoic acid were also eliminated in urine. At 24 hours post-dosing, 90% of the radioactivity recovered in feces was un-metabolized parent compound. Other compounds identified in the feces were 3-phenoxybenzoic acid, 3-(4-hydroxyphenoxy)benzoic acid, 4-hydroxy-cis-cypermethrin and trans-hydroxy-cis-cypermethrin. Elimination: Following a single oral low dose, elimination of *cis* or *trans* cypermethrin was rapid, with 90% of the administered dose eliminated within 48 hours (primarily via urine; 50% to 70%). Following exposure to an acute high dose of cypermethrin, urinary elimination accounted for 30% to 53% of the administered dose, while fecal elimination accounted for up to 59% of the administered dose. Elimination in expired

Study/Species	Results/Effects
	air was low for all dose regimens. **Repeated Low Dose (28 Days):** Twenty-four hours after the last dose, no sex-related differences were noted in the distribution of radioactivity to tissues. The concentration of radioactivity ranged from 4.1 to 5.1 µg/g in fat and 0.49-0.91 µg/g in liver, kidney, ovary, adrenal, skin, GI tract and carcass. Levels of radioactivity were low in the brain in both sexes, and male testes. **Repeated Low Dose (70 Days):** Twenty-four hours after the first dose, the highest levels of radioactivity were detected in fat (0.21 µg/g) and liver (0.19 µg/g). Radioactivity levels increased rapidly in all tissues during the first week of exposure, followed by a slower increase during subsequent weeks. Peak levels of radioactivity in blood and most tissues were noted on treatment day 56 while peak levels in fat (3.91 µg/g) and ovary (0.03 µg/g) were detected on day 49. Peak levels in the sciatic nerve were low. After cessation of treatment, radioactivity levels decreased rapidly in most tissues, reaching background levels within 8 to 15 days, with the exception of fat and skin. Fifty days after the last exposure, the concentration of radioactivity in fat was 0.32 µg/g. After cessation of treatment, the predominant isomer detected in fat was cis-cypermethrin (88%); the trans-isomer accounted for 12%. The elimination of cypermethrin from fat was biphasic due to the initial rapid elimination of trans-cypermethrin, followed by the slower elimination of the cis-isomer. Elimination half-lives in adipose tissue were 18 days and 3 days for the cis- and trans- isomers, respectively. ***Potential for bioaccumulation***
Distribution Elimination – Intravenous Injection (Cypermethrin) Wistar Rats PMRA#1789424	Distribution: Rapid distribution, with peak levels observed in most tissues (except fat) within 1-hour post-treatment. At 1-hour post-dosing, the highest levels of radioactivity were detected in the liver, kidney and ovaries, while the lowest levels were detected in brain, spinal cord and sciatic nerve. Levels in fat peaked 4-hours post-dosing and decreased slowly; the half-life in fat was > 24 hours. 24-Hours post-dosing, levels in most tissues decreased rapidly (except fat and skin), with half-lives ranging from 4.8 to 9 hours. At 24 hours post-dosing, elimination was notably slow in skin (half-life = 12.8 hours), likely due to the high fat content. At 120 hours post-dosing, levels were still present in fat (1.45 µg/g) and skin (0.15 µg/g). Elimination: Elimination in urine and feces was rapid, with 57% and 80% of the administered radioactivity recovered in ♀ within 24 hours and 48 hours, respectively. After 120 hours, urinary elimination of radioactivity accounted for 61% of the administered dose, while fecal elimination accounted for 28% of the administered dose.

Study/Species	Results/Effects
Acute Oral Toxicity – Gavage (Cypermethrin) CD Mice	**Supplemental** Corn Oil: LD_{50} = 88 mg/kg bw (♂/♀) ***High acute oral toxicity*** DMSO: LD_{50} = 1126 mg/kg bw (♂/♀) ***Slight acute oral toxicity*** 50% Aqueous Suspension: LD_{50} = 657 mg/kg bw (♂/♀) ***Moderate acute oral toxicity***
Acute Oral Toxicity - Gavage (Cypermethrin) Wistar Rats PMRA#1203062	LD_{50} = 247/309 mg/kg bw (♂/♀) (in corn oil) **≥ 150 mg/kg bw**: mortality, clinical signs of neurotoxicity, gait abnormalities ***High acute oral toxicity***
Acute Toxicity - Gavage (Zeta-Cypermethrin) Sprague-Dawley Rats PMRA#1789382	LD_{50} = 134/86.0 mg/kg bw (♂/♀) (in corn oil) **≥ 50 mg/kg bw/day (♀):** mortality, clonic convulsions, tremors, splayed hindlimbs, loss of muscle control, vocalization, abdominogenital staining, bloody oral discharge, grinding teeth, nasal discharge, chromodacryorrhea, chromorhinorrhea, ↓ feces, ↓ locomotion, unthriftiness **≥ 100 mg/kg bw/day:** rales; mortality, tremors, clonic convulsions, loss of muscle control, splayed hindlimbs, abdominogenital staining, bloody oral discharge, diarrhea, grinding teeth, nasal/oral discharge, chromorhinorrhea (♂); ataxia (♀) **≥ 150 mg/kg bw/day:** hypersensitivity to touch, vocalization (♂); diarrhea (♀) ***High acute oral toxicity***
Acute Toxicity – Gavage (Zeta-Cypermethrin) Sprague-Dawley Rats PMRA#1789383	LD_{50} = 269/285 mg/kg bw (♂/♀) (in corn oil) **≥ 100 mg/kg bw/day:** clinical signs of toxicity **≥ 200 mg/kg bw/day:** mortality ***High acute oral toxicity***
Acute Toxicity – Gavage (Zeta-Cypermethrin)	LD_{50} = 557/1264 mg/kg bw (♂/♀) (undiluted) **≥ 500 mg/kg bw/day (♂):** clinical signs of toxicity, mortality

Study/Species	Results/Effects
Sprague-Dawley Rats PMRA#1789384	**≥ 1000 mg/kg bw/day:** clinical signs of neurotoxicity ***Moderate acute oral toxicity***
Acute Comparative Oral Toxicity - Gavage (Cypermethrin) Rats	**Supplemental** LD_{50} = 163 mg/kg bw in 3-wk old rats (in DMSO) LD_{50} = 322 mg/kg bw in 6-wk old rats (in DMSO) LD_{50} = 526 mg/kg bw in 12-wk old rats (in DMSO) ***Age-related sensitivity to mortality***
Acute Comparative Oral Toxicity – Gavage (Cypermethrin) Wistar Rats PMRA#2220432	LD_{50} = 15 mg/kg bw in 8-day old rats (in corn oil) LD_{50} = 27 mg/kg bw in 16-day old rats (in corn oil) LD_{50} = 49 mg/kg bw in 21-day old rats (in corn oil) LD_{50} = 250 mg/kg bw in adult rats (in corn oil) Clinical signs of neurotoxicity (seizures, tremors, choreoathetosis, uncoordinated movement, pawing and burrowing, facial licking, extensive grooming) were observed in all age groups. Salivation was noted in PND 21 and adult rats. ***Age-related sensitivity to mortality***
Acute Dermal Toxicity (Cypermethrin) Wistar Rats PMRA#1203062	LD_{50} > 4920 mg/kg bw (♂/♀) (undiluted) Subdued behaviour, unsteady/altered gait, piloerection, ungroomed appearance and urinary incontinence were noted. ***Low acute dermal toxicity (non-abraded)***
Acute Dermal Toxicity (Cypermethrin) New Zealand White Rabbits PMRA#1203062	LD_{50} > 2460 mg/kg bw (♂/♀) (undiluted) Lacrimation, ocular discharge and tremors were noted. Cypermethrin was slightly irritating to rabbit skin. ***Low acute dermal toxicity (abraded)***
Acute Inhalation Toxicity (Cypermethrin) Rats	**Supplemental** LC_{50} = 2.5 mg/L

Study/Species	Results/Effects
	Clinical signs of neurotoxicity ***Low acute inhalation toxicity***
Primary Eye Irritation (Cypermethrin) New Zealand White Rabbits PMRA #1203062	Slight redness of conjunctivae, chemosis and discharge (persisted to day 7). ***Slight ocular irritant***
Primary Skin Irritation (Cypermethrin) New Zealand White Rabbits PMRA #1203062	Slight to mild erythema on intact and abraded skin in all animals (reversed after 48 hours). Primary Irritation Index: 0.71 ***Slight dermal irritant***
Dermal Sensitization – Buehler Method (Cypermethrin) Dunkin Hartley Guinea-Pigs PMRA #1203062	**Supplemental** Negative ***Not a dermal sensitizer***
Short-Term Toxicity Studies	
28-Day Oral Toxicity – Diet (Cypermethrin) Swiss Mice PMRA#1961908	**Supplemental** **≥ 196/189 mg/kg bw/day (♂/♀):** ↑ hepatic microsomal APDM activity, ↑ SER proliferation (not assessed at 600/719 mg/kg bw/day), ↑ hepatic centrilobular hypertrophy; ↑ relative liver wt *(♀); considered to be an adaptive response* **600/719 mg/kg bw/day (♂/♀):** ↓ bw, ↓ bwg, ↑ relative liver wt, liver histopathology ('glycogen-like' vacuolation with ↑ eosinophilia)
28-Day Oral Toxicity – Diet (Zeta-Cypermethrin) Range-Finding Study	**Supplemental** **≥ 69/74mg/kg bw/day (♂/♀):** ↓ food consumption, abdominal staining, ataxia, chromorhinorrhea, ↓ feces, dehydration, splayed hind limbs, unthriftiness; ↓ bw (♀) **105/102 mg/kg bw/day (♂/♀):** 100% mortality (day 7 to day 9), tremors,

Study/Species	Results/Effects
F344 Rats	convulsions, hypersensitivity to touch
5-Week Oral Toxicity – Diet (Cypermethrin) Non-Guideline Sprague-Dawley Rats PMRA#1258260	**NOAEL = 50 mg/kg bw/day** **LOAEL = 150 mg/kg bw/day**, based on ↓ bw, ↑ relative liver wt; ↑ ALP activity, ↑ packed cell volume, ↑ RBC count (♂); ↑ relative kidney wt (♀)
5-Week Oral Toxicity – Diet (Cypermethrin) Non-Guideline Sprague-Dawley Rats PMRA#1258261	**NOAEL = 15 mg/kg bw/day** **LOAEL = 37.5 mg/kg bw/day**, based on ataxia, sensitivity to sound and touch, ↓ growth, ↑ relative liver wt; ↓ plasma protein, ↑ urea, ↑ potassium (♂) **75 mg/kg bw/day (♂/♀):** mortality, coagulative necrosis in liver, swelling, axonal breaks, myelin degeneration and vacuolation in sciatic nerve
13-Week Oral Toxicity - Diet (Cypermethrin) Sprague-Dawley Rats	**NOAEL = 37.2/45 mg/kg bw/day** **LOAEL = 116/132 mg/kg bw/day**, based on↓ bwg and food consumption, mortality (during first 4 wks), staggered gait, splayed hindlimbs, tremors, loss of muscle coordination, hypersensitivity, abdominal staining, ↓ RBC volume and count; ↑ ALT (♂); clonic convulsions, ↑ ALT, ↓ serum albumin, ↑ BUN, ↑ plasma potassium, slight ↑ relative liver wt (♀)
13-Week Oral Toxicity - Diet (Zeta-Cypermethrin) F344 Rats PMRA #1789385	**NOAEL = 16.7/19.7 mg/kg bw/day** **LOAEL = 33.7/38.4 mg/kg bw/day**, based on ↓ bw, ↓ bwg, ↓ food consumption, ↓ blood glucose, ↑ relative brain wt; ↓ ALT, ↓ AST, ↑ relative testes wt (♂); interference of estrous cycle, ↑ relative kidney wt (♀) **68.0/79.5 mg/kg bw/day (♂/♀):** mortality, abdominal-genital staining, ataxia, clonic convulsions, dehydration, hypersensitivity to touch and sound, splayed hindlimbs, recumbency, unthriftiness, walking on toes; ↓ leukocytes, ↓ RBC, ↓ Hct, ↓ Hgb, ↑ BUN (♂)
13-Week Oral Toxicity - Diet (Cypermethrin)	**NOAEL = 40 mg/kg bw/day** **LOAEL = 160 mg/kg bw/day**, based on ↓ mean bw and food intake throughout treatment, ↑ plasma urea, splayed limbs, "nervousness"; ↓ MCH, ↓ MCV, ↑

Study/Species	Results/Effects
Wistar Rats PMRA#1258265	prothrombin time, ↑ relative kidney wt (♂); ↑ relative liver wt (♀)
13-Week Oral Toxicity - Diet (Cypermethrin) Sprague-Dawley Rats PMRA#1204016 PMRA#1258264	**NOAEL = 40 mg/kg bw/day** **LOAEL = 160 mg/kg bw/day**, based on ataxia, splayed limbs, hypersensitivity to sound and touch, ↓ bw and food consumption, ↑ plasma urea, microscopic changes in sciatic nerve (axonal breaks, vacuolation); mortality, ↑ plasma potassium (♂); ↓ Hgb, ↓ packed cell volume, ↓ RBC count, ↑ plasma protein, ↑ ALP (♀)
13-Week Oral Toxicity - Diet (Cypermethrin) Wistar Rats PMRA#1203067 PMRA#1789386 PMRA#1789387	**Supplemental** **≥7.5 mg/kg bw/day:** ↑ proliferation of hepatic SER, ↑ hepatic APDM activity (reversed after recovery) (♂/♀); slight ↑ myeloid:erythroid ratio in bone marrow (♀); *not considered biologically adverse* **75 mg/kg bw/day:** ↓ bw, ↓ bwg, ↓ food consumption, ↑ liver wt; mitochondrial swelling of myelinated axons (♂)
28-Day Oral Toxicity - Diet (Cypermethrin) Beagle Dogs PMRA#1961871 PMRA#1961872 PMRA#1961874	**Supplemental** **≥ 29.3/28.8 mg/kg bw/day (♂/♀):** ↓ food consumption; ↓ bw, ↓ bwg (♂) **≥30.3/37.5 mg/kg bw/day (♂/♀):** tremors, ↓ bw, ↓ bwg **41.8/43.4 mg/kg bw/day (♂/♀):** ataxia, irregular gait, lethargy, heavy breathing, vomiting, ↓ ALT activity
6-Week Oral Toxicity – Capsule (Cypermethrin) Beagle Dogs	**Supplemental** **≥25 mg/kg bw/day:** ↓ bwg, ↓ food consumption, tremors, incoordination, gastrointestinal disturbances, liver enzyme induction **50 mg/kg bw/day**: convulsions, liver histopathology ("fatty changes") (♂)
13-Week Oral Toxicity - Diet	**NOAEL = 12.5 mg/kg bw/day** **LOAEL = 37.5 mg/kg bw/day**, based on ↓ bw, body tremors, exaggerated gait, ataxia, incoordination, hyperaesthesia, licking/chewing of paws, diarrhea, anorexia

Study/Species	Results/Effects
(Cypermethrin) Beagle Dogs PMRA#1203067	
13-Week Oral Toxicity - Diet (Cypermethrin) Beagle Dogs PMRA#1789388	**NOAEL = 20.7/25.4 mg/kg bw/day** **LOAEL = 24.6/34.3 mg/kg bw/day**, based on ↓ food consumption; tremors (♂); ↓ bw, ↓ bwg (♀) **37.0/45.2 mg/kg bw/day (♂/♀):** ↓ bw, ↓ bwg; ↓ testes wt (♂); tremors (♀)
12-Month Oral Toxicity - Diet (Cypermethrin) Beagle Dogs PMRA#1789389	**NOAEL = 6.0/5.7 mg/kg bw/day** **LOAEL = 20.4/18.1 mg/kg bw/day**, based on ↓ bw, ↓ bwg; mortality, irregular gait, tremors, salivation (♂); ↓ food consumption (♀) **33.9/38.1 mg/kg bw/day (♂/♀):** ↓ food consumption, prostration, ↓ activity, incoordination, clonic convulsions, unthrifty coat, alopecia, ↓ testes wt (♂); ↓ food consumption;tremors, irregular gait, ↑ vocalization (♀)
12-Month Oral Toxicity - Capsule (Cypermethrin) Beagle Dogs PMRA#1203057 PMRA#1203222	**NOAEL = 5 mg/kg bw/day** **LOAEL = 15 mg/kg bw/day**, based on vomiting, ↓ bwg, irregular gait, body tremors, incoordination, excitability, disorientation, hypersensitivity to noise
21-Day Dermal Toxicity (Zeta-Cypermethrin) Sprague-Dawley Rats	**Dermal LOAEL = 100 mg/kg bw/day**, based on erythema, eschar; desquamation at the site of application (♀) **Systemic NOAEL ≥1000 mg/kg bw/day**

Study/Species	Results/Effects
21-Day Dermal Toxicity (Cypermethrin) New Zealand White Rabbits PMRA#1202064 PMRA#1203049	**Dermal and Systemic NOAEL (Non-abraded) ≥ 200 mg/kg bw/day** **Dermal and Systemic NOAEL (Abraded) = 20 mg/kg bw/day**, based on slight to severe dermal irritation, hepatic focal necrosis; ↓ testes wt (♂); ↓ bw (♀)
21-Day Inhalation Toxicity (Nose-Only) (Cypermethrin) Wistar Rats	**NOAEL = 2.7 mg/kg bw/day** **LOAEL = 13.6 mg/kg bw/day (0.05 mg/L/day)**, based on ↓ bw, ↓ bwg, ↓ food consumption, salivation
Neurotoxicity Studies	
Acute Oral Neurotoxicity – Gavage (Cypermethrin) Non-Guideline Motor Activity Long-Evans Rats PMRA#2007554	**$BMDL_{20}$ = 5.2 mg/kg bw**, based on ↓ motor activity (exponential dose-response modeling BMD_{20} = 7.9 mg/kg bw)

Study/Species	Results/Effects
Acute Oral Neurotoxicity – Gavage (Cypermethrin) Non-Guideline Locomotor Activity and Acoustic Startle Response Long-Evans Rats PMRA#2220433	**LOAEL = 30 mg/kg bw**, based on ↓ locomotor activity, ↓ peak amplitude of acoustic startle response, ↑ latency to onset of acoustic startle response, ↓ sensitization of acoustic startle response
Acute Oral Neurotoxicity – Gavage (Cypermethrin) Non-Guideline Sprague-Dawley Rats PMRA#2007556 PMRA#2043579	**LOAEL = 65 mg/kg bw**, based on salivation, head held low, abnormal gait, walking on tiptoes, splayed/dragging hindlimbs, hunched body, slight tremors, low arousal, no startle response, ↓ rotarod performance, ↓ forelimb grip strength **≥ 100 mg/kg bw (♂):** ↓ bw, ↑ biting, clonic convulsions, abdominal staining, soiled fur, ataxia, impaired mobility and gait, head flick, no olfactory orientation, ↓ air righting reflex (lands on side), no hindlimb extension, ↓ hindlimb resistance and grip strength, catalepsy, ↓ body temperature **150 mg/kg bw (♂):** splayed hindlimbs, red deposits around mouth, body drag, no reaction to approach or touch, altered tail pinch response, no air righting reflex (lands on back), ↓ olfactory orientation
Acute Oral Neurotoxicity - Gavage (Cypermethrin) Non-Guideline Charles River Rats	**LOAEL = 100 mg/kg bw**, based on signs of intoxication (*details not provided*); dose-related axonal breaks in sciatic nerve (♀) **≥200 mg/kg bw:** mortality, swelling of myelin sheath in sciatic nerve **400 mg/kg bw:** course tremors, bleeding from nose, spasmodic
Acute Oral Neurotoxicity - Gavage (Cypermethrin)	**NOAEL = 30 mg/kg bw** **LOAEL = 100 mg/kg bw**, based on ataxia, staggered or impaired gait, limp condition, splayed hindlimbs, ↓ motor activity, uncoordinated landing during righting reflex; abnormal posture, oral discharge (♂); whole body tremors, localized spasms/twitching, walking on toes, salivation, lacrimation, abdomino-genital staining (♀) **200 mg/kg bw:** mortality, abdomino-genital staining, ↓ locomotion; inability to walk,

Study/Species	Results/Effects
Sprague-Dawley Rats PMRA#1789402 PMRA#1789403	↑ landing foot splay (♂); oral discharge, abnormal posture, exaggerated hindlimb flexion, exaggerated startle response, ↓ tail-flick latency (♀)
Acute Oral Neurotoxicity - Gavage (Cypermethrin) Non-Guideline Long-Evans Rats PMRA#2220434	**Supplemental** **≥ 20 mg/kg bw**: ↓ motor activity (more pronounced in ♀); abnormal gait, ↓ hind-limb grip strength (♂); ↓ touch response (♀) **≥ 60 mg/kg bw**: salivation, chorcoathetosis, urination, ↓ arousal, abnormal motor activity, splayed limbs, flattened posture, ↓ forelimb grip strength, ↑ landing foot splay, altered righting reflex; ↓ touch response, ↓ tail pinch response (♂); ↓ hind-limb grip strength, abnormal gait, ↓ tail pinch response (♀) **120/100 mg/kg bw:** ↑ mortality, ↓ bw
Acute Oral Neurotoxicity – Gavage (Zeta-Cypermethrin) Long-Evans Rats PMRA#1789404	**NOAEL = 10 mg/kg bw** **LOAEL = 50 mg/kg bw**, based on soiled fur, tremors; abdomino-genital staining, splayed hind limbs, oral discharge, staggered gait, ↑ latency to tail-flick (♂); abnormal mobile posture, severely impaired gait, unable to walk, salivation, convulsions, exaggerated auditory response, landing on back during righting reflex (♀) **250 mg/kg bw:** ataxia, ↓ locomotion, ↑ vocalizations, uncoordinated landing during righting reflex, ↓ activity, loss of muscle control, lacrimation, absent righting reflex, ↑ latency to tail flick, rigidity or limpness during handling; abnormal posture, impaired gait, convulsions (♂); lacrimation, oral discharge, mortality, loss of muscle control, splayed hindlimbs, dragging hind limbs (♀)
13-Week Oral Neurotoxicity - Diet (Cypermethrin) Sprague-Dawley Rats PMRA#1789405 PMRA#1789408	**NOAEL = 31/37 mg/kg bw/day** **LOAEL = 77/95 mg/kg bw/day**, based on ↓ bw, ↓ bwg; ↓ food consumption, ↑ landing foot splay (♂); ataxia, splayed hindlimbs, staggered gait, impaired gait, abnormal posture, ↓ feces (♀) **102/121 mg/kg bw/day (♂/♀):** ataxia, slight to moderate gait impairment, uncoordinated landing during righting reflex, splayed hindlimbs, staggered gait, unthrifty appearance, abnormal posture, localized spasms/twitching, ↓ fore-limb grip strength, ↓ hind-limb grip strength (♂); tremors, ↓ food consumption, ↑ landing foot splay, ↓ motor activity (♀)

Study/Species	Results/Effects
13-Week Oral Neurotoxicity - Diet (Zeta-Cypermethrin) Long-Evans Rats PMRA#1789409	**NOAEL = 5/31.5 mg/kg bw/day** **LOAEL = 26.3 mg/kg bw/day**, based on ↓ food consumption; ↑ landing foot splay, ↓ bw, ↓ bwg (♂) **47.2/55.6 mg/kg bw/day (♂/♀):** ↑ tail flick latency (♂); ↓ bw, ↓ bwg (♀)
Developmental Neurotoxicity - Diet (Cypermethrin) Rats	**Supplemental** **<u>Maternal Toxicity</u>:** No treatment-related effects. **<u>Offspring Toxicity</u>:** **17.3 mg/kg bw/day**: ↓ bw; marginal/suggestive changes in brain morphometry (♀); *additional data were not available*
Developmental Neurotoxicity – Diet (Zeta-Cypermethrin) Sprague-Dawley Rats PMRA#1961891 PMRA#1961892	**Supplemental** **<u>Maternal Toxicity:</u>** No adverse effects. **<u>Offspring Toxicity:</u>** **≥ 3.5 mg/kg bw/day**: ↓ motor activity (♂) **≥20.8 mg/kg bw/day:** ↓ bw; ↓ motor activity (♀)
Developmental Neurotoxicity - Gavage (Cypermethrin) Non-Guideline CD-1 Mice PMRA#2220435	**<u>Parental Toxicity</u>** **NOAEL = 5 mg/kg bw/day** **LOAEL = 10 mg/kg bw/day**, based on clinical signs of toxicity during treatment which persisted during mating (salivation, hyperactivity, tremors); ↓ bw during gestation and lactation, ↓ number of pregnant mice, mortality during treatment (before mating), ↓ bwg (♀) **<u>Offspring Toxicity</u>** **NOAEL = 5 mg/kg bw/day** **LOAEL = 10 mg/kg bw/day**, based on ↓ number of pups, ↓ number of litters, ↓ number of pups/litter, ↓ number of live pups/litter, ↑ dead pups/litter, ↓ bw (PND 0-28), ↓ bwg, delayed pinna detachment, delayed down appearance, delayed eye opening, ↓ reflex performance, ↑ mean latency to re-orient (geotaxis), ↓ locomotion, ↓ social interaction, ↓ development of swimming behavior, ↓ cliff avoidance performance, altered open field activity

Study/Species	Results/Effects
Developmental Neurotoxicity - Diet (Zeta-Cypermethrin) Sprague-Dawley Rats PMRA#1961877 PMRA#1961878 PMRA#1961881 PMRA#1961887 PMRA#1961888 PMRA#1961889 PMRA#1961911	**Maternal Toxicity:** **NOAEL = 9 mg/kg bw/day** **LOAEL = 21.1 mg/kg bw/day**, based on ↓ bw during lactation, ↓ bwg during gestation and lactation, ↓ food consumption during lactation **Offspring Toxicity:** **NOAEL = 9 mg/kg bw/day** **LOAEL = 21.1 mg/kg bw/day**, based on ↓ bw, ↓ bwg, ↑ total and ambulatory motor activity; ↓ fore-limb grip strength, ↓ hind-limb grip strength, ↑ total and ambulatory motor activity due to ↓ habituation, ↓ learning and memory, ↑ relative brain wt (♂); ↓ hind-limb grip strength, ↓ total and ambulatory motor activity, ↑ thickness of cerebral cortex, ↑ thickness of pons (♀) Concentrations of zeta-cypermethrin in maternal milk were proportional to intake. At LD 4, relatively high concentrations of cypermethrin in maternal milk (3.9 to 11.5 ppm) were present in dams receiving dietary doses ≥ 125 ppm. Concentrations were slightly lower in fetal plasma (0.11-0.14 ppm), compared to maternal plasma (0.3-0.57 ppm) in all groups on GD 20. Fetal plasma levels did not correlate with maternal dietary levels, suggesting limited placental transfer.
Delayed Neurotoxicity - Gavage (Cypermethrin) Domestic Hens	**Supplemental** No treatment-related clinical signs or histopathological lesions were noted.
Delayed Neurotoxicity - Gavage (Cypermethrin) Domestic Hens PMRA#1203708	**NOAEL = 2500 mg/kg bw/day** **LOAEL = 5000 mg/kg bw/day**, based on ↓ bw, ↓ food consumption **10,000 mg/kg bw/day:** ↑ disruption, fragmentation and distortion of axons in the spinal cord (in the absence of neurotoxic signs)
Chronic Toxicity/Carcinogenicity Studies	
101-Week Chronic Toxicity and Carcinogenicity - Diet (Cypermethrin) Swiss Mice PMRA#1789394 PMRA#1789395 PMRA#1789396	**NOAEL = 57 mg/kg bw/day** **LOAEL = 229 mg/kg bw/day**, based on ↓ bw, ↓ bwg, ↓ food consumption, ↓ Hgb, ↓ Hct, ↓ RBC, ↓ MCV, ↓ MCH, ↓ platelets, ↓ neutrophils, ↑ relative liver wt; ↓ testes wt at interim sacrifice (♂) There was an increased incidence of lung adenomas in females. The incidence in ♀ receiving 0, 0, 100, 400 or 1600 ppm was 4/61 (7%), 4/60 (7%), 6/61 (10%), 7/60 (12%) or **13/60 (22%)** **; **p<0.01

Study/Species	Results/Effects
PMRA#1171353 PMRA#1171361	***Evidence of tumorigenicity***
2-Year Chronic Toxicity/ Carcinogenicity – Diet (Cypermethrin) Wistar Rats PMRA#1789391 PMRA#1789396 PMRA#1203053 PMRA#1203052 PMRA#1203056 PMRA#1961905 PMRA#1961907	**NOAEL = 7.3/7.4 mg/kg bw/day** **LOAEL = 72.5/72.1 mg/kg bw/day**, based on ↓ bw, ↓ bwg, ↓ food consumption, ↓ Hgb, ↓ Hct, ↓ MCV, ↓ MCH, ↑ prothrombin time, ↓ cholesterol, ↓ triglycerides, ↑ BUN, ↓ urine volume, ↑ urine specific gravity, clinical signs during wk 1 (frequent face-washing, lack of coordination in hindlimbs, sensitivity to sound), thin appearance, hair loss, ↓ neutrophils, ↓ monocytes, ↑ renal pelvic calcification; tubular atrophy of testes in decedents (♂); ↑ total WBC, ↑ lymphocytes, ↑ liver wt, ↑ nephrocalcinosis and thickening of pelvic epithelium of the kidney (♀) There was an increased incidence of Leydig cell tumors. The incidence in ♂ receiving 0, 0, 0.7, 7.3 or 72.5 mg/kg bw/day was 11%, 13%, 11%, 11% or 20%, respectively. Historical control range = 0 to 60% Historical control mean = 13.7% ***Evidence of tumorigenicity***
Developmental/Reproductive Toxicity Studies	
3-Generation Reproductive Toxicity - Diet (Cypermethrin) Wistar Rats PMRA#1789397 PMRA#1789399 PMRA#1203232 PMRA#1203233 PMRA#1203234 PMRA#1203236	**<u>Parental Toxicity</u>** **NOAEL = 7.5 mg/kg bw/day** **LOAEL = 50.0/37.5 mg/kg bw/day**, based on ↓ food consumption and ↓ bwg in F_0, F_1 and F_2, ataxia, uncoordinated movement, ↑ sensitivity to touch and sound, piloerection, trembling, hunched appearance, salivation and high stepping gait in F_0; mortality in 1 F_0 ♂ with severe neurological disturbances, testicular tubular atrophy in F_1 and F_2 (♂); ↓ bwg in F_1 (♀)↑ **<u>Offspring Toxicity</u>** **NOAEL = 7.5 mg/kg bw/day** **LOAEL = 50.0/37.5 mg/kg bw/day**, based on ↓ pup bw in F_1 and F_2, ↓ litter wt gain in F_1, F_2 and F_3 **<u>Reproductive Toxicity</u>** No reproductive effects.

Study/Species	Results/Effects
3-Generation Reproductive Toxicity - Diet (Cypermethrin) Wistar Rats PMRA#1212115 PMRA#1171362 PMRA#1254878	**Supplemental** **Parental Toxicity** **25 mg/kg bw/day:** ↓ bwg, ↓ food consumption **Offspring Toxicity** **25 mg/kg bw/day:** ↓ pup bwg in both generations, ↓ litter size and litter wt in F_{1a} throughout lactation **Reproductive Toxicity** **25 mg/kg bw/day:** ↓ litter size in F_{1a} at birth
2-Generation Reproductive Toxicity - Diet (Zeta-Cypermethrin) Sprague-Dawley Rats PMRA#1789398	**Parental Toxicity** **NOAEL = 5.9/6.4 mg/kg bw/day** **LOAEL = 22.1/24.2 mg/kg bw/day**, based on ↓ bw/bwg (F_1), hypersensitivity to sound (F_1), ↓ food consumption (F_0, F_1), ↑ relative brain wt (F_0); ↓ bw/bwg F_0, emaciation (F_0) (♀) **43.4/47.8 mg/kg bw/day** (♂/♀): ataxia, clonic convulsions, tail injuries related to convulsions (F_0 and F_1), whole body tremors (F_1); ↓ bw/bwg (F_0) (♂); 2 deaths during lactation (preceded by hypersensitivity to noise, ataxia and emaciation), urine-stained abdominal fur, bedding in the mouth, gastric erosion (F_0) (♀) **Offspring Toxicity** **NOAEL = 5.9/6.4 mg/kg bw/da** **LOAEL = 22.1/24.2 mg/kg bw/day**, based on ↓ bw (F_1, F_2) **43.4/47.8 mg/kg bw/day in F_1 pups only** (♂/♀): ↑ pup deaths (Days 2-28), ↑ complete litter loss, ↓ lactation indices, clinical signs (ataxia, tremors, hypersensitivity to sound, weakness, pale, cold to touch, dehydrated), dried red staining around mouth, urine-stained abdominal fur, small testes, gaseous distension of GI tract, GI bleeding (black-brown viscous fluid), urinary tract bleeding **Reproductive Toxicity** The highest dose was not maintained over both generations due to excessive mortality at 750 ppm in the F_1 generation. The following parameters were not assessed: estrous cycle and sperm measurements; brain, liver, kidney, spleen, pituitary, thyroid and adrenal weights in F_0 generation; quantitative assessment of primordial follicles; number of corpora lutea, resorptions (early and late); sexual maturation; F_2 offspring organ wts. ***No evidence of sensitivity of the young***

Study/Species	Results/Effects
Developmental Toxicity - Gavage (Cypermethrin) Sprague-Dawley Rats PMRA#1789411	**Maternal Toxicity:** **NOAEL = 35 mg/kg bw/day** **LOAEL = 70 mg/kg bw/day**, based on ↓ bw during gestation, mortality, ataxia, splayed limbs, spasms, hypersensitivity to noise, convulsions **Developmental Toxicity:** **NOAEL ≥70 mg/kg bw/day** ***No evidence of developmental toxicity or sensitivity of the young***
Developmental Toxicity - Gavage (Cypermethrin) Sprague-Dawley Rats PMRA#1789410 PMRA#1961912 PMRA#1961903	**Maternal Toxicity:** **NOAEL = 12.5 mg/kg bw/day** **LOAEL = 25 mg/kg bw/day**, based on ataxia, urine and fecal stained fur, ↓ bw, ↓ bwg, ↓food consumption **35 mg/kg bw/day:** hypersensitivity, emaciated appearance, excess salivation, soft or liquid feces **Developmental Toxicity:** **NOAEL ≥ 35 mg/kg bw/day** ***No evidence of developmental toxicity or sensitivity of the young***
Developmental Toxicity - Gavage (Cypermethrin) New Zealand White Rabbits PMRA#1789414 PMRA#1961902	**Maternal Toxicity:** **NOAEL = 100 mg/kg bw/day** **LOAEL = 450 mg/kg bw/day**, based on pink/red staining of cage pan liner, 1 doe sacrificed on GD 26 after aborting entire litter, ↓ feces, ↓ bwg **700 mg/kg bw/day**: abdominogenital staining, anorexia, ataxia, 1 doe sacrificed after displaying swelling, scabbing and severe ulceration of the vaginal area **Developmental Toxicity:** **NOAEL ≥ 700 mg/kg bw/day** ***No evidence of developmental toxicity or sensitivity of the young***

Study/Species	Results/Effects
Developmental Toxicity – Gavage (Cypermethrin) New Zealand White Rabbits	**Supplemental (range-finding study)** **Maternal Toxicity:** **≥ 750 mg/kg bw/day**: abdominal spasms, diarrhea, ataxia, anorexia, nasal discharge, unthriftiness, ↓ feces, abdomino-genital staining, red or pink staining of pan liner, dose-related abortion **Developmental Toxicity:** No adverse effects.
Genotoxicity Studies	
In-Vitro Reverse Mutation (Cypermethrin) Non-Guideline S. typhimurium TA-1538, E. coli WP2 uvr, E. coli WP2 PMRA#1204017	Negative
In-Vitro Reverse Mutation (Zeta-Cypermethrin) S. typhimurium TA-100, TA-98, TA-1535, TA-1537, TA-1538 PMRA#1789418	Negative
In-Vitro Gene Mutation (Zeta-Cypermethrin) Chinese Hamster Ovary (CHO) Cells HGPRT locus PMRA#1789419	Negative (insoluble > 100 µg/mL)
In-Vitro Mouse Lymphoma Assay (Zeta-Cypermethrin) L5178Y cell line	**Supplemental** Negative
In-Vitro Chromosomal Aberrations and Sister Chromatid Exchange	**Supplemental**

Study/Species	Results/Effects
(Cypermethrin) Non-Guideline Swiss Mouse Spleen Cells PMRA#2220436	**≥ 0.25 µg /mL:** ↑ chromosomal aberrations, ↑ sister chromatid exchange ***Positive for chromosomal aberrations and sister chromatid exchange in mouse spleen cells***
In-Vitro DNA Adducts and Crosslinks (Cypermethrin) Non-Guideline Mouse Hepatocytes Calf Thymus PMRA#2220437	**≥ 0.78 µg/mL:** ↑ DNA monoadducts, ↑ interstrand crosslinks Interstrand crosslinks were not formed with calf thymus DNA or hepatocytes treated with SKF:525A, a cytochrome P450 inhibitor. ***Positive for induction of adducts and cross links in mouse hepatocytes***
In-Vitro Chromosomal Aberrations (Zeta-Cypermethrin) CHO Cells PMRA#1789421	Negative
In-Vitro Unscheduled DNA Synthesis (Zeta-Cypermethrin) F344 Rat Hepatocytes PMRA#1789420	Negative
In-Vitro DNA Damage – Comet Assay	**≥ 1000 µM:** ↑ DNA damage (↑ tail length, ↑ tail DNA, ↑ tail moment) **10,000 µM**: slight cytotoxicity

Study/Species	Results/Effects
(Cypermethrin) CHO Cells PMRA#2220438	***Positive for DNA damage in CHO cells***
In-Vitro DNA Damage – Comet Assay (Cypermethrin) Human Peripheral Lymphocytes PMRA#2324423	**200 µg /mL:** ↑ DNA damage (↑ tail length, ↑ tail intensity, ↑ tail moment) ***Positive for DNA damage in human lymphocytes***
In-Vitro DNA Damage – Comet Assay (Cypermethrin) Human Peripheral Lymphocytes PMRA#2220439	**10 µM:** ↑ DNA damage ***Positive for DNA damage in human lymphocytes***
In-Vitro Chromosomal Aberrations and Sister Chromatid Exchange – (Cypermethrin) Non-Guideline Human Peripheral Lymphocytes PMRA#2324424	No increase in the frequency of chromosomal aberrations or sister chromatid exchange. **≥ 10 µg/mL**: altered cell cycle (↓ cell proliferative rate index) ***Negative for DNA damage in human lymphocytes***
In-Vitro Micronuclei (Cypermethrin)	**200 µg/mL**: ↑ frequency of total micronuclei and bi-nucleated cells with micronuclei in whole blood cultures but not in isolated lymphocyte cultures

Study/Species	Results/Effects
Human Lymphocytes PMRA#2220441	***Equivocal for induction of micronuclei in human lymphocytes***
In-Vivo Chromosomal Aberrations - Gavage (Cypermethrin) Chinese Hamster Bone Marrow Cells	Negative
In-Vivo Chromosomal Aberrations - Gavage (Cypermethrin) Non-Guideline Swiss Mouse Bone Marrow Cells PMRA#2220443	**Supplemental** **50 mg/kg bw**: ↑ chromatid gaps, breaks and fragments ***Positive for chromosomal aberrations in mouse bone marrow cells***
In-Vivo Chromosomal Aberrations – I.P. Injection (Cypermethrin) Non-Guideline Swiss Mouse Spleen & Bone Marrow Cells PMRA#2220436	**Supplemental** **180 mg/kg bw**: ↑ chromosome aberrations in spleen and bone marrow cells 6-hours after treatment. ***Positive for chromosomal aberrations in mouse spleen and bone marrow cells***
In-Vivo Sister Chromatid Exchange – I.P. Injection (Cypermethrin) Non-Guideline	**Supplemental** **180 mg/kg bw:** ↑ sister chromatid exchange

Study/Species	Results/Effects
Swiss Mouse Bone Marrow Cells PMRA#2220436	***Positive for sister chromatid exchange in mouse bone marrow cells***
In-Vivo Micronuclei – Diet or Dermal (Cypermethrin) Non-Guideline Swiss Mouse Bone Marrow Cells PMRA#2220444	**Supplemental** ***Oral Exposure*** **≥ 300 ppm**: ↑ frequency of polychromatic erythrocytes **900 ppm**: ↑ frequency of micronuclei ***Dermal Exposure***: **360 mg/kg bw/day**: mortality, signs of acute toxicity, ↑ frequency of micronuclei ***Positive for micronuclei induction***
In-Vivo Chromosomal Aberrations - Gavage (Zeta-Cypermethrin) Sprague-Dawley Rat Bone Marrow Cells PMRA #1789422	Negative
In-Vivo Dominant Lethal Mutation - Oral (Cypermethrin) CD-1 Mice	Negative
In-Vivo Unscheduled DNA Synthesis (Cypermethrin) F344 Rat Hepatocytes	Negative

Study/Species	Results/Effects
In-Vivo DNA Damage - Comet Assay (Cypermethrin) D. melanogaster larvae PMRA#2220459	**≥ 0.002 ppm**: ↑ DNA damage (↑ tail length, tail moment and tail DNA). ***Positive for DNA damage in D. melanogaster***
Special Studies – Non-Guideline	
5-Day Oral Neurotoxicity - Gavage (Cypermethrin) Chinese Hamsters PMRA#2220448	**Supplemental** **≥ 5 mg/kg bw/day**: ↑ beta-galactosidase activity; dose-related ↓ performance in mean slip angle test (♀) **20 mg/kg bw/day**: ↓ growth; ↓ performance in mean slip angle test (♂); hyper-excitability (♀)
5-Day Oral Neurotoxicity - Gavage (Cypermethrin) Chinese Hamsters PMRA#2220448	**Supplemental** **30 mg/kg bw/day:** transient dermal irritation, skin ulceration, unusual gait, ↓ performance in incline-plane test (slip angle test), ↑ beta-glucuronidase activity and ↑ beta-galactosidase activity in peripheral nerve tissues
14-Day Oral Toxicity - Gavage (Cypermethrin) Wistar Rats Specialized study of apoptosis in cortical astrocytes from young rats PMRA#2220446	**Supplemental** **<u>In Vivo Assay:</u>** **≥ 10 mg/kg bw/day (♂):** ↑ apoptotic index **<u>In-Vitro Assay:</u>** Cypermethrin promoted a time- and concentration-related ↑ in apoptosis via early and irreversible inactivation of EGFR signalling, and reduced synthesis of HB-EGF. Pre-treatment with heparin-binding-EGF protected astrocytes from cypermethrin-induced apoptosis.
Oral Post-Natal Male Reproductive Toxicity - Gavage	**Supplemental**

Study/Species	Results/Effects
(Cypermethrin) ICR Mice Specialized study of male reproductive effects PMRA#2220450	**<u>Maternal Toxicity:</u>** No signs of maternal toxicity. **<u>Offspring Toxicity:</u>** **25 mg/kg bw/day:** *PND 21:* ↓ testes wt, ↓ serum testosterone, ↓ testicular testosterone, ↓ mRNA and protein levels of P450scc (a testosterone biosynthetic enzyme) in the testes, microscopic changes in the testes (↓ layers of spermatogenic cells, ↑ inside diameters of seminiferous tubules, disturbed array of spermatogenic cells in testes). *PND 70:* microscopic changes in the testes (↓ layers of spermatogenic cells, ↑ inside diameters of seminiferous tubules, disturbed array of spermatogenic cells in testes), ↓ testes wt, ↓ number of spermatozoa, slight ↓ in testicular StAR and testosterone biosynthetic enzymes
Short-Term Oral Male Reproductive Toxicity - Gavage (Cypermethrin) 5-Week Old CD-1 Mice Specialized study of male reproductive effects PMRA#2220452	**LOAEL = 25 mg/kg bw**, based on ↓ number of spermatozoa in cauda epididymides, ↑ apoptotic cell index in testes, ↑ inside diameter of seminiferous tubules, "disturbed array" of spermatogenic cells in testes, ↓ serum and testicular testosterone levels, ↓ expression of testicular StAR
Short-Term Oral Male Reproductive Toxicity - Gavage (Cypermethrin Formulation) Adult Swiss Mice Specialized study of male reproductive effects PMRA#2220453	**Supplemental** **<u>Male Reproductive Effects</u>** **≥ 1.38 mg/kg bw/day (♂):** dose-related ↓ epididymal spermatozoa count, dose-related ↑ spermatozoa with abnormal head shape following exposure for 6 or 12 wks **<u>Fertility Indices</u>** **≥ 1.38 mg/kg bw/day (♂/♀):** ↓ mean litter wt and viability index following 12 wk exposure **≥ 2.76 mg/kg bw/day (♂/♀):** ↓ mean litter wt following 6 wk exposure **<u>6-Week Recovery</u>** **≥ 2.76 mg/kg bw/day (♂):** ↑ spermatozoa with abnormal head shape following 12 wk exposure **5.52 mg/kg bw/day(♂):** ↓ epididymal spermatozoa count following 12 wk exposure
Short-Term Oral Male Reproductive Toxicity - Gavage	**Supplemental**

Study/Species	Results/Effects
(Cypermethrin) Adult Sprague-Dawley Rats PMRA#2220457	**≥ 6.25 mg/kg bw/day (♂):** ↓ number of seminiferous tubules, ↑ tubular degeneration, dose-related atrophy and distortion of seminiferous tubules, ↑ ultrastructural changes in seminiferous tubules (swollen mitochondria, widened ER and Golgi apparatus, disrupted cellular junctions) **≥ 12.5 mg/kg bw/day (♂):** ↓ number of cell layers in seminiferous tubules, ↓ androgen receptor expression in Leydig, Sertoli and Peritubular cells in testes **≥ 25 mg/kg bw/day (♂):** ↓ prostate wt, ↓ liver wt, ↓ kidney wt, ↓ testes wt **50 mg/kg bw/day (♂):** ↓ serum testosterone, ↑ serum FSH and LH, ↓ testicular daily sperm production, reduction and deformation of spermatogonia and spermatocytes, distorted arrangement of spermatoblasts
In-Vivo Oxidative Stress (Cypermethrin) Swiss Albino Mice PMRA#2324426	↑ serum AST and ALT, ↑ lipid peroxidation, ↓ GSH (in whole blood, liver, kidney, heart), degenerative histopathology in the heart, liver and kidney following exposure to 10 mg/kg bw/day cypermethrin Treatment with cypermethrin and 5 to 20 mg/kg bw/day thymoquinone resulted in a dose-related reversal of serum ALT and AST levels, lower levels of urea, cholesterol, triglycerides and ↑ glucose and HDL-cholesterol. Thymoquinone also ↓ severity of degenerative histopathological changes in the heart, liver and kidney, compared to animals receiving cypermethrin alone.
In-Vitro Anti-Androgenic and Androgenic Activity (Cypermethrin) Androgen-Receptor Mediated Reporter Gene Assay CV-1 African Green Monkey Kidney Cells PMRA#2324427	Weak anti-androgenic activity with cypermethrin and 3-phenoxybenzoic acid in vitro. No evidence of androgenic activity with cypermethrin or 3-phenoxybenzoic acid.

Study/Species	Results/Effects
In-Vitro Anti-Androgenic and Androgenic Activity (Cypermethrin) Androgen-Receptor Mediated Reporter Gene Assay (Luciferase) MDA-kb2 Cells PMRA#2324694	**Supplemental** Cypermethrin induced anti-androgenic activity in MDA-kb2 cells in vitro. β-cypermethrin did not exhibit anti-androgenic activity.
In-Vivo Hershberger Assay (Cypermethrin) 3-week old Sprague-Dawley rats PMRA#2324694	**Supplemental** **50 mg/kg bw/day:** ↓ seminal vesicle, ventral prostate and dorsolateral prostate weights β-cypermethrin did not significantly reduce the weight of androgen-dependent tissues.

Appendix III Dietary Exposure and Risk Estimates for Cypermethrins

Table 1 Dietary Exposure and Risk Estimates for Cypermethrins

Population Subgroup	Acute Dietary[1] (99.9th Percentile)				Chronic Dietary[2]		Cancer Dietary[3]	
	Food Only		Food + Water		Food + Water		Food + Water	
	Exposure (mg/kg bw)	%ARfD	Exposure (mg/kg bw)	%ARfD	Exposure (mg/kg bw/d)	%ADI	Exposure (mg/kg bw/d)	Risk
General Population	0.004690	23	0.004778	24	0.000181	<1	0.000181	1E-06
All Infants (<1 year old)	**0.013938**	**70**	**0.014002**	**70**	0.000435	2	N/A	
Children 1-2 years old	0.008192	41	0.008389	42	**0.000628**	**3**		
Children 3-5 years old	0.007384	37	0.007490	37	0.000457	2		
Children 6-12 yrs old	0.004574	23	0.004567	23	0.000261	1		
Youth 13-19 yrs old	0.003991	20	0.003992	20	0.000149	<1		
Adults 20-49 yrs old	0.004458	22	0.004532	23	0.000131	<1		
Adults 50+ years old	0.004073	20	0.004167	21	0.000127	<1		
Females 13-49 years old	0.003347	17	0.003412	17	0.000128	<1		

[1]Acute Reference Dose (ARfD) of 0.02 mg/kg bw applies to the general population and all population subgroups.

[2]Acceptable Daily Intake (ADI) of 0.02 mg/kg bw/day applies to the general population and all population subgroups.

[3]Cancer Potency Factor ($q1^*$) of 8.09×10^{-3} $(mg/kg\ bw/day)^{-1}$.

Appendix IV Food Residue Chemistry Summary

Metabolism in Livestock and Plants

The nature of the residue in animal and plant commodities is adequately understood based on metabolism studies in lactating cows, laying hens, apple, bean foliage, cabbage, cotton, lettuce, maize and sugar beet. Cypermethrin was ^{14}C-labelled in either the cyclopropyl or the benzyl ring carbon positions. The major degradation pathway in plants is similar to the one found in animals. It starts with the ester cleavage of the parent molecule to yield *cis* and *trans* 3-(2,2-dichlorovinyl)2,2 dimethylcyclopropane carboxylic acid (*cis* and *trans* DCVA) and 3-phenoxybenzaldehyde (3-PBAldehyde). This latter metabolite is further oxidized or reduced to the corresponding 3-phenoxybenzoic acid (3-PBAcid) or 3-phenoxybenzyl alcohol (3-PBAlcohol) and their hydroxylated products, followed by conjugation. Much of the residue was readily excreted. The main component of the residue in milk, fat and eggs was the parent compound. In muscle, liver and kidney, levels of DCVA and 3-PBAcid and conjugates were oftentimes greater than those of the parent. The residue was fat soluble. When applied to a crop, very little cypermethrin is absorbed or translocated. The highest residue level occurs on parts of the plant exposed to direct application and, to a great extent, consists of unchanged cypermethrin. Exposed residues are subject to isomerisation, presumably by a photolytic process.

Residue Definition

Plants – In most of the metabolism studies in plants, unchanged cypermethrin was the predominant residue, accounting for more than 50% of the total radioactive residue (TRR) in apple peel and pulp, lettuce leaves, sugar beet foliage and roots, and maize fodder and silage. The metabolites 3-PBAcid and DCVA and their conjugates were found at levels >10% TRR in some cases. However, it is not expected that these metabolites (except for those with the electrophilic dichlorovinyl group) will be of significant toxicological concern. Moreover, in those crops where DCVA was found at >10% TRR, the detected levels were very low, close to the limit of quantitation (LOQ).

Livestock – The DCVA levels in animal tissues, liver and kidney were greater than those of the parent. However, considering that these are secondary residues and that these animal commodities contribute little to the total dietary exposure, the contribution of DCVA residue to the exposure would be negligible.

Water – With regard to the environmental fate, available studies indicated that parent compound was stable at neutral pH.

Parent cypermethrin was therefore considered as a valid indicator of the level of cypermethrins in plant and animal commodities as well as in drinking water, in accordance with the current residue definition (RD), which is expressed as cypermethrin *per se* (sum of isomers). The RD is explicitly expressed as the sum of cypermethrin isomers in order to take into account the various mixtures of cypermethrin isomers available on the world market (alpha-, zeta-, theta-cypermethrin, etc.), given that current residue monitoring methods cannot differentiate the individual cypermethrins. This RD is used for both enforcement and dietary risk assessment purposes.

Analytical Methodology

Adequate analytical methods have been developed for the determination of cypermethrin residues in plant and animal commodities. These methods are gas chromatographic (GC) with electron capture (EC) or mass spectrometric (MS) detection methods and are all adaptations, with a few minor modifications, of the current USEPA enforcement methods that appear as Methods I and II in Pesticide Analytical Manual (PAM) Volume II. Method I has a detection limit of 0.01 ppm, and Method II has detection limits of 0.005 ppm for milk and 0.01 ppm for livestock tissues. These methods are not stereospecific: no distinction is made between residues of the different cypermethrins. The methods were adequately validated in conjunction with the analysis of field and processing samples. Cypermethrin is also listed as a compound that can be measured by the Canadian Food Inspection Agency (CFIA)'s multiresidue analytical method.

Magnitude of the Residue

Cypermethrin MRLs have been established on the basis of adequate field trial residue data for a range of crops/commodities. Some of these MRLs have been translated to cypermethrin from petitioned and subsequently established import MRLs for zeta-cypermethrin, which is not registered for use in Canada. Zeta-cypermethrin is registered in the US on the same agricultural crops as cypermethrin plus many more crops. When applied on agricultural crops, the typical use rate for *zeta*-cypermethrin is approximately one-half that for cypermethrin because the concentration of the most insecticidally active isomers is approximately two times higher in *zeta*-cypermethrin than in cypermethrin. Cypermethrin residues in/on a few commodities are regulated under Subsection B.15.002(1) of the *Food and Drugs Regulations* (General MRL) not to exceed 0.1 ppm. Established MRLs are accessible through Health Canada's MRL Database.

Crop Rotation Studies

A submitted confined crop rotation study showed TRRs > 0.01 ppm in several rotational crops at 120 days plant back interval (PBI). The subsequently submitted field crop rotational study indicated that residues of cypermethrin and its metabolites were non-detectable (<0.01 ppm) in/on the rotational crop commodities of leafy vegetables, root and tuber vegetables, and cereal grain crops that were planted at 30 days PBI. This sudy supports a 30-day PBI which is, therefore, proposed to be implemented on Canadian labels, as is the case for US labels. The following statement is proposed to be added on Canadian cypermethrin labels under Directions of Use:

"Crop Rotation: rotational crops may not be planted within 30 days after the last application, except crops on which cypermethrin is registered (listed on this label)."

Processing Studies

Processing studies with cypermethrin or companion isomers (alpha- and zeta-cypermethrin) have been submitted to and reviewed by the PMRA and/or other regulatory agencies. Because of the common composition of the three compounds, a food processing factor obtained for residues of one compound was assumed to apply to the residues of the others. The experimental processing factors were used in the dietary exposue and risk assessment.

Residue Data for Food in Food Handling Establishments and Warehouses

Several cypermethrin formulations are registered in the US and elsewhere for use in non-food/non-feed areas of food handling establishments and warehouses or as household insecticides. Sufficient restrictions are included on the labels of such products to prevent exposure of food and feed. Non-detectable to 0.01 ppm (LOQ) cypermethrin residues were reported in studies on file. The USEPA has established a cypermethrin tolerance of 0.05 ppm on food/feed commodities (other than those covered by a higher tolerance as a result of use on growing crops) in food/feed handling establishments. This use is not on Canadian labels, but needs to be considered for import purposes. The PMRA used the US tolerance for risk assessment purposes.

Livestock, Poultry, Egg and Milk Residue Data

Residues of cypermethrin can occur in milk, eggs and livestock tissues and organs due to registered uses on agricultural crops, some of which may be used as livestock feed items. In addition, cypermethrin is currently registered for direct livestock treatments (ear tag use in Canada, dermal application in other countries) that can also contribute to the residues. Based on available data, Canadian MRLs have been established for residues of cypermethrin in animal commodities (see MRL Database).

Data Gaps – No deficiencies were identified in the residue chemistry database with regard to currently registered uses of cypermethrin. No further data are required for continued registration.

Appendix VAgricultural Mixer/Loader/Applicator and Postapplication Risk Assessment

Table 1 Occupational Mixer/Loader/Applicator Non-Cancer Exposure and Risk Assessment

Crop	Application Equipment	ATPD[a] (ha/day unless specified)	Amount Handled[b] (kg a.i./ha)	Dermal MOE[c] (Target = 300)	Inhalation MOE[d] (Target = 300)
BASELINE PPE: Single layer (long-sleeved shirt, long pants), chemical-resistant gloves; open mixer/loader; open cab (all except aerial)					
Sunflower; potato; canola; corn	Aerial	400	11.40 – 28.49	3922 – 51908	4738 – 270772
Apple; grape; nectarine; peach; pear; plum	Airblast	20	1.20 – 2.04	735 – 1246	9938 – 16854
Sunflower; summer fallow (headlands); barley; wheat; potato; canola; corn; evening primrose	Groundboom	360	9.00 – 25.64	2649 – 7548	3290 – 9375
Tobacco; tomato; asparagus; celery; stevia; rutabaga, turnip; cole crops; lettuce; onion; carrot; strawberry; seedlings or transplants (carrots, cole crops, conifer and onions)		26	0.91 – 3.70	18341 – 74649	22781 – 92720
Tobacco - greenhouse; stevia; seedlings or transplants (carrots, cole crops and onions); conifer seedling (nursery)*; roadsides**	MPHG MPHW Backpack	150 – 3800***	0.01 – 2.66	385 – 504776	538 – 398230
Strawberry	MPHG	3800***	1.29 – 3.80	269 – 794	376 – 1110
	MPHW/Backpack	150 – 3800***	0.05 – 0.15	6995 – 119063	23188 – 31858
Roadsides**	Right-of-Way	3800***	0.98	6286	33253
MID-LEVEL PPE: Coverall over a single layer (long-sleeved shirt, long pants), chemical-resistant gloves					
Strawberry	MPHG	3800	1.29 – 3.80	613 – 1807	376 – 1110

MPHG = mechanically-pressurized handgun; MPHW = manually-pressurized handwand.

* For conifer seedling (nursery), the label states to not use backpack.

** For roadsides, backpack and right-of-way equipment are assumed to be used.

*** Units in L/day.

[a] Area treated per day; default areas from the PMRA ATPD table were used.

[b] Amount Handled Per Day = Application Rate (kg a.i./ha or kg a.i./L) × Area Treated per Day (ha or L)

[c] MOE = margin of exposure. Dermal MOE = NOAEL (mg/kg bw/day)/Dermal Exposure (mg/kg bw/day); based on oral DNT NOAEL of 5 mg/kg bw/day (for all exposure durations) and target MOE of 300; Dermal Exposure (mg/kg bw/day) = [Unit Exposure (PHED or AHETF µg/kg a.i. handled) × Conversion Factor of 0.001 (mg/µg) × Application Rate (kg a.i./ha or kg a.i./L) × Area Treated per Day (ha or L) × Dermal Absorption (7%)]/Body weight (80 kg). Shaded cells (in grey) indicate MOEs that are less than the target MOE.

[d] Inhalation MOE = NOAEL (mg/kg bw/day)/Inhalation Exposure (mg/kg bw/day); based on an inhalation NOAEL of 2.7 mg/kg bw/day (for all exposure durations) and target MOE of 300. Inhalation Exposure (mg/kg bw/day) = [Unit Exposure (PHED or AHETF µg/kg a.i. handled) × Conversion Factor of 0.001 (mg/µg) × Application Rate (kg a.i./ha or kg a.i./L) × Area Treated per Day (ha or L)]/Body weight (80 kg).

Table 2 Occupational Mixer/Loader/Applicator Cancer Exposure and Risk Assessment (Baseline PPE)

Crop	Application Equipment	ATPD[a] (ha/day unless specified)	Amount Handled[b] (kg a.i./ha)	Cancer Risk[c]
BASELINE PPE: Single layer (long-sleeved shirt, long pants), chemical-resistant gloves; open mixer/loader; open cab (all except aerial)				
Sunflower; potato; canola; corn	Aerial	318	9.06 – 22.65	1E-08 – 5E-07
Apple; grape; nectarine; peach; pear; plum	Airblast	7	0.42 – 0.71	5E-07 – 8E-07
Sunflower; summer fallow (headlands); barley; wheat; potato; canola; corn; evening primrose	Groundboom	240	6 – 17.10	2E-07 – 6E-07
Tobacco; tomato; asparagus; celery; stevia; rutabaga, turnip; cole crops; lettuce; onion; carrot; strawberry; seedlings & transplants (carrots, cole crops, conifer and onions)		12	0.42 – 1.71	8E-09 – 4E-08
Tobacco - greenhouse; stevia; seedlings & transplants (carrots, cole crops and onions); conifer seedling (nursery)*; strawberry; roadsides**	MPHG MPHW Backpack	150 – 3800***	0.01 – 2.66	6E-09 – 9E-06
Roadsides**	Right-of-Way	3800***	0.98	3E-07

MPHG = mechanically-pressurized handgun; MPHW = manually-pressurized handwand.

* For conifer seedling (nursery), the label states to not use backpack.

** For roadsides, only backpack and right-of-way are assumed to be used.

*** Units in L/day.

[a] Area treated per day; default areas from the PMRA ATPD table were used.

[b] Amount Handled Per Day = Application Rate (kg a.i./ha or kg a.i./L) × Area Treated per Day (ha or L)

[c] Cancer Risk = Lifetime Average Daily Dose (mg/kg bw /day) × q_1* (0.00809 (mg/kg bw/day)$^{-1}$), with:

- Lifetime Average Daily Dose (mg/kg bw /day) = [(Absorbed Daily Dose × Exposure Days (30 or 15 days/year) × Working Duration (40 years)] / [(365 (days/year) × Life Expectancy (78 years)].
- Absorbed Daily Dose (mg/kg bw/day) = Dermal Exposure (mg/kg bw/day) + Inhalation Exposure (mg/kg bw/day).
- Dermal Exposure (mg/kg bw/day) = [Unit Exposure (PHED or AHETF µg/kg a.i. handled) × Conversion Factor of 0.001 (mg/µg) × Application Rate (kg a.i./ha or kg a.i./L) × Area Treated per Day (ha or L) × Dermal Absorption (7%)]/Body Weight (80 kg)
- Inhalation Exposure (mg/kg bw/day) = [Unit Exposure (PHED or AHETF µg/kg a.i. handled) × Conversion Factor of 0.001 (mg/µg) × Application Rate (kg a.i./ha or kg a.i./L) × Area Treated per Day (ha or L)]/Body Weight (80 kg).

Table 3 Occupational Postapplication Non-Cancer Exposure and Risk Assessment*

Activity	Applications Rate[a] (kg a.i./ha)	Transfer Coefficient[b] (cm^2/hr)	DFR[c] (µg/cm^2)	Dermal Exposure[d] (µg/kg bw/day)	MOE[e] (Target 300)	REI[f]
Corn (Sweet) – Maximum of 3 applications/year with a minimum interval of 7 days						
Harvesting (Hand)	0.07	8800	0.3040	18.73	267	12 hour
Corn (Sweet) – Maximum of 3 applications/year with a minimum interval of 4 days						
Harvesting (Hand)	0.07	8800	0.3651	22.49	222	12 hour
Corn (Sweet) – Maximum of 2 applications/year with a minimum interval of 4 days						
Harvesting (Hand)	0.07	8800	0.2898	17.85	280	12 hour
Grape – Maximum of 3 applications/year with a minimum interval of 7 days						
Girdling, Turning	0.06	19300	0.2561	34.59	145	12 hour
Risk Mitigation Measures using Longer REI						
Corn (Sweet) – Maximum of 3 applications/year with a minimum interval of 7 days						
Harvesting (Hand)	0.07	8800	0.2462	15.17	330	5 days
Corn (Sweet) – Maximum of 3 applications/year with a minimum interval of 4 days						
Harvesting (Hand)	0.07	8800	0.2662	16.40	305	5 days
Corn (Sweet) – Maximum of 2 applications/year with a minimum interval of 4 days						
Harvesting (Hand)	0.07	8800	0.2608	16.07	311	5 days
Grape – Maximum of 3 applications/year with a minimum interval of 7 days						
Girdling, Turning	0.06	19300	0.1225	16.55	302	7 days

* For all other crops and activities, which are not listed in this table, a 12-hour REI was determined. Cancer risks at the required REIs are not of concern.

[a] Maximum label application rate.

[b] From Agricultural Reentry Task Force (2008).

[c] DFR= dislodgeable foliar residue. The default peak DFR value of 25% of the application rate with 10% dissipation rate was assumed.

[d] Dermal exposure (µg/kg bw/day) = DFR (µg/cm^2) × TC (cm^2/hr) × Duration (8 hrs/day) × Dermal Absorption (7%)/Body Weight (80 kg).

[e] MOE = margin of exposure. MOE = NOAEL (mg/kg bw/day)/Exposure (mg/kg bw/day). Dermal MOEs are based on an oral DNT NOAEL of 5 mg/kg bw/day and target MOE of 300. Shaded cells (in grey) indicate MOEs that are less than the target MOE.

[f] Restricted entry interval.

Table 4 Non-Cancer Exposure and Risk Estimates for Residential Postapplication Exposure from Fruit Trees

Scenario	Lifestage	TC[a] (cm^2/hr)	Exposure Time (hrs)	Dermal Exposure[b] (mg/kg bw/day)	Dermal MOE[c] (Target = 300)
Apple – Application rate: 101.75 g a.i./ha					
Residential Trees	Adults 16 < 80 years old	1700	1.0	0.00065	7741
	Youth 11 < 16 years old	1400	1.0	0.00075	6697
	Children 6 < 11 years old	930	0.5	0.00044	11320

[a] Transfer coefficients for youth 11< 16 years old and children 6 < 11 years old were calculated from the adult 16< 80 years old TC value adjusted for body surface area using an adjustment factor of 0.82 (1.59 m^2/1.95 m^2) and 0.55 (1.08 m^2/1.95 m^2), respectively (USEPA, 2012)

[b] Estimated dermal exposure on the day of cypermethrin application to apple trees (day zero) in mg/kg bw/day, calculated using the following formula: DFR (0.254 µg/cm^2) × Conversion Factor of 0.001 (mg/µg) × TC (cm^2/hr) × Exposure Time (1 hr for adults and youth; 0.5 hr for children) × Dermal Absorption (7%)/ Body Weight (80 kg for adults; 57 kg for youth; 32 kg for children)

[c] Based on oral DNT NOAEL of 5 mg/kg bw/day (for short-term scenario) and target MOE of 300.

Table 5 Cancer Exposure and Risk Estimates for Residential Postapplication Exposure from Fruit Trees

Scenario	Lifestage	TC[a] (cm^2/hr)	ADD[b] (mg/kg bw/day)	Years of Exposure	LADD[c] (mg/kg bw/day)	Lifetime Cancer Risk[d]
Apple – Application rate: 101.75 g a.i./ha						
Residential Trees	Adults 16 < 80 years old	1700	0.000206	63	0.0000157	1.E-07
	Youth 11 < 16 years old	1400	0.000238	5		
	Children 6 < 11 years old	930	0.000141	5		

[a] Transfer coefficients for youth 11 < 16 years old and children 6 < 11 years old were calculated from the adult TC value adjusted for body surface area using an adjustment factor of 0.82 (1.59 m^2/1.95 m^2) and 0.55 (1.08 m^2/1.95 m^2), respectively (USEPA, 2012)

[b] Absorbed Daily Dose (mg/kg bw/day) = DFR (0.254 µg/cm^2) × TC (cm^2/hr) × Conversion Factor of 0.001 (mg/µg) × Exposure Time (1 hr for adults and youth; 0.5 hr for children) × Dermal Absorption (7%)/ Body Weight (80 kg for adults; 57 kg for youth; 32 kg for children).

[c] Lifetime Average Daily Dose (mg/kg bw /day) = $\sum_i$ [(ADD*i* (mg/kg bw/day) × Exposure Frequency (5 days/year) × Years of Exposure (63 years for adults, 5 years for youth, and 5 years for children)] / [365 (days/year) × Life Expectancy (78 years)].

[d] Cancer Risk = $\sum_i$ LADD*i* (mg/kg bw/day) × q_1* (0.00809 (mg/kg bw/day)$^{-1}$).

i = Exposure estimate for the lifestage.

Table 6 Aggregate Cancer Exposure and Risk Estimates from Dietary and Residential Postapplication Exposure

Lifestage	Dermal			Dietary (food & drinking water)			Aggregate Cancer Risk[g]
	Absorbed Daily Dose[a] (mg/kg bw/day)	Lifetime Average Daily Dose[b] (mg/kg bw/day)	Cancer Risk[c]	Chronic Daily Intake[d] (mg/kg bw/day)	Lifetime Average Daily Intake[e] (mg/kg bw/day)	Cancer Risk[f]	
Adults (16 < 80 years old)	0.000206	0.0000157	1E-07	0.000130	0.000168	1E-06 [1.36E-06]	1E-06 [1.49E-06]
Youth (11 < 16 years old)	0.000238			0.000180			
Children (6 < 11 years old)	0.000141			0.000281			
Children (1 < 6 years old)	Not required			0.000520			

[a]Dermal Absorbed Daily Dose (mg/kg bw/day) = DFR (time-weighted average of 0.138 µg/cm^2) × TC (cm^2/hr) × Conversion Factor of 0.001 (mg/µg) × Exposure Time (1 hr for adults and youth; 0.5 hr for children) × Dermal Absorption (7%) / Body Weight (80 kg for adults; 57 kg for youth; 32 kg for children).

[b]Dermal Lifetime Average Daily Dose expressed in mg/kg bw /day, calculated using the following formula:

Dermal LADD = $\sum_i i$ = Dermal Absorbed Daily Dose$_i$ (mg/kg bw/day) × Exposure Frequency$_i$ (30 days/year) × Years of Exposure$_i$ (63 years for adults; 5 years for youth, and 5 years for children) / 365 (days/year) × Life Expectancy (78 years)

Note that the LADD is a lifetime estimate and should only be presented for the general population, not for each individual lifestage.

[c]Dermal Cancer Risk = Dermal Lifetime Average Daily Dose (mg/kg bw/day) × q_1* (0.00809 (mg/kg bw/day)$^{-1}$)

[d]Dietary Chronic Daily Intake from food and drinking water for custom subpopulations generated using DEEM-FCID™

[e]Dietary Lifetime Average Daily Intake = $\sum_i i$ = Dietary Chronic Daily Intake$_i$ (mg/kg bw/day) × Years of Exposure$_i$ (63 years for adults; 5 years for youth, and 5 years for children) / Life Expectancy (78 years)

[f]Dietary Cancer Risk = Dietary Lifetime Average Daily Intake (mg/kg bw/day) × q_1* (0.00809 (mg/kg bw/day)$^{-1}$)

[g]Aggregate Cancer Risk = Dermal Cancer Risk + Dietary Cancer Risk

i = Exposure estimate for the lifestage.

Table 7 Non-Cancer Exposure and Risk Assessment of Cypermethrin Based on Biological Monitoring Data

Subpopulation	Daily Exposure[a] (mg/kg bw/day)	Aggregate MOEs[bc] (Target = 300)
Canadian Health Measures Survey (CHMS)[d]		
General Population	0.000488	10238
Children 3-5 years old	0.001190	4201[e]
Children 6-10 years old	0.000222	22573
Youth 11-15 years old	0.000646	7745[e]
Adults 16-79 years old	0.000523	9558
Maternal Infant Research on Environmental Chemicals-Child Development Plus (MIREC-CD Plus)[e]		
Children <3 years old	0.000632	7909

[a] Daily Exposure was calculated using the following equation: Daily Exposure (mg/kg bw/day) = [(urinary metabolite concentration from CHMS and MIREC × daily excretion (g creatinine/day) × (molecular weight parent/ molecular weight metabolite)] / [urinary excretion fraction from human pharmacokinetic studies × body weight]
[b] MOE = Margin of Exposure; MOEs were calculated using the following equation: MOE = NOAEL (mg/kg bw/day)/Daily Exposure (mg/kg bw/day); based on oral DNT NOAEL of 5 mg/kg bw/day (for all exposure durations) and target MOE of 300.
[c] MOEs for 'cis+trans-DCCA' metabolite concentration. The urinary excretion fraction for cis-DCCA was used, as it is lower than that of trans.
[d] The 95th percentile was used in the non-cancer risk assessment, except for those sub-populations where the coefficient of variation (CV) was greater than 33%, then the upper 95% confidence bound on the 95th percentile was used (children 3-5 years old and youth 11-15 years old). DCCA metabolites were used instead of 3-PBA as they have fewer contributing parent pyrethroids.
[e] The 95th percentile was used in the non-cancer risk assessment.

Table 8 Cancer Risk Assessment of Cypermethrin Based on Biological Monitoring Data

Subpopulation	Daily Exposure[a] (mg/kg bw/day)	Years of Exposure	Lifetime Average Daily Exposure[b] (mg/kg bw/day)	Cancer Risk[c]
Population 6 - <80 years old	0.000130	74	0.000122	1E-06
Children <6 years old	0.000242	5		

[a] Daily Exposure was calculated using the following equation: Daily Exposure (mg/kg bw/day) = [urinary metabolite concentration from CHMS × daily excretion (g creatinine/day) × (molecular weight parent/ molecular weight metabolite)] / [urinary excretion fraction from human pharmacokinetic studies × body weight]
[b] Lifetime Average Daily Exposure was calculated for the population aged 6 - <80 years old and children <6 years old using the following equation: Lifetime Average Daily Exposure (mg/kg bw/day) = $\sum_i$ [Daily Exposure$_i$ (mg/kg bw/day) × Years of Exposure (74 years for the population aged 6 - <80 years old, 5 years for children <6 years old) / Life Expectancy (79 years)].
[c] Cancer risk was calculated using the following equation:
Cancer Risk = Lifetime Average Daily Exposure (mg/kg bw/day) × q_1^* (0.00809 (mg/kg bw/day)$^{-1}$)
i = Exposure estimate for the lifestage.

Appendix VI Environmental Assessment

Table 1 Summary of Fate Processes for Cypermethrin in the Terrestrial Environment

Process	$T_{1/2}$ or DT_{50}	DT_{90}	Kinetics	Comments	PMRA#
Abiotic transformation					
Hydrolysis 25°C, 30 days	pH 5: Stable pH 7: Stable pH 9: 1.8 - 2.5 d	nr	nr	May be an important route of transformation under alkaline conditions	PMRA 2350160
Phototransformation on fine sandy loam soil (76% sand, 13% silt, 11% clay, 1.8%OM, pH 6.9)	128-219 d	nr	nr	Not a major route of transformation	PMRA 2350160
Biotransformation					
Biotransformation in aerobic fine sandy loam soil (76% sand, 13% silt, 11% clay, 1.8% OM, pH 6.9)	60-61 d	nr	nr	Moderately persistent	PMRA 2350160
Biotransformation in aerobic 3.3% O.C., 59.7% coarse sand, 24.4% fine sand, 4.0% silt, 12.0% clay, pH 6.4, CEC 11.9	49 d	462 d	DFOP	Moderately persistent	PMRA 1244815
Biotransformation in aerobic 7% O.C., 57.3% course sand, 22.7% fine sand, 9.1% silt. 10.8% clay, pH 7.7, C.E.C. 6.0	20 d	67 d	SFO	Slightly persistent	PMRA 1244815
Biotransformation in anaerobic fine sandy loam soil (76% sand, 13% silt, 11% clay, 1.8% OM, pH 6.9)	53-63 d	nr	nr	Moderately persistent	PMRA 2350160
Mobility					
Adsorption - cypermethrin	Tavares sand	K_d = 657	K_{oc} = 328 500	immobile	PMRA 2350160
	Thurston sandy loam	K_d = 1160	K_{oc} = 134 900		
	Georgetown silty loam	K_d = 1900	K_{oc} = 82 600		
	Troy grove clay loam	K_d = 416	K_{oc} = 20 800		

Process	$T_{1/2}$ or DT_{50}	DT_{90}	Kinetics	Comments	PMRA#
Adsorption – 3-phenoxybenzoic acid (3-PBA)	Silty clay	$K_d = 3.1$	$K_{oc} = 122$	Medium - high mobility	PMRA 2350160
	Sandy loam	$K_d = 0.98$	$K_{oc} = 118$		
	Sandy loam	$K_d = 2.4$	$K_{oc} = 215$		
Adsorption – (trans-DCVA)	Silty clay	$K_d = 0.46$	$K_{oc} = 18$	Very high mobility	PMRA 2350160
	Sandy loam	$K_d = 0.16$	$K_{oc} = 19$		
	Sandy loam	$K_d = 0.54$	$K_{oc} = 48$		
Soil leaching	Approximately 73-93% of the applied radioactivity remained in the upper 15 cm layer of a sandy loam soil column; however, up to 13.2% of the applied radioactivity leached out of the soil column in the form of DCVA.				PMRA 2350160
	More than 99% of the ^{14}C-residue in clay loam, loamy sand, coarse sand and peat soil columns remained within the top (0-5cm) treated soil segment after leaching with 67.5 cm rain water. Leaching below 5cm occurred only in the coarse sand soil and fen peat soils and was 0.4 and 0.3% of applied radioactivity respectively.				PMRA 1244880
Terrestrial Field studies					
Madera California silt loam soil (78-82% sand, 14-20% silt, 2-4% clay, 0.2-0.6% OM, pH 6.5-7.2)	13 d	nr	nr	Non-persistent	PMRA 2350160
Cheneyville Loisiana loamy sand soil (30% sand, 64% silt, 6% clay, 0.7% OM, pH 7.0)	5 d	nr	nr	Non-persistent	PMRA 2350160
London Ont. mineral and organic soils (soil properties not reported)	30 d	nr	nr	Slightly persistent	PMRA 1171367
Goldsboro, NC Loamy fine sand	10 d	33 d	SFO	Non-persistent	PMRA 1244819
Champaign Ilinois Silty clay loam	12 d	1245 d	IORE	Non-persistent	PMRA 1244819
Visalia, CA Fine sandy loam	3 d	18 d	IORE	Non-persistent	PMRA 1244819
Vicksburg, MS Silty loam	1.3 d	9 d	IORE	Non-persistent	PMRA 1244819

Table 2 Summary of Fate Processes for Cypermethrin in the Aquatic Environment

Process	$T_{1/2}$ or DT_{50}	DT_{90}	Kinetics	Comments	PMRA#
Abiotic transformation					
Hydrolysis 25°C, 30 days	pH 5: Stable pH 7: Stable pH 9: 1.8 - 2.5 d	nr	nr	May be an important route of transformation under alkaline conditions	PMRA 2350160
Phototransformation in pH 7 buffered solution	20-36 d	nr	nr	Not a major route of transformation	PMRA 2350160
Biotransformation					
Aerobic water-clay loam soil system (water pH 7.6, organic carbon not reported; soil pH 5.2-6.5, organic matter 2.7%) 25°C, 30 days	Whole system : 7.04 d	Whole system : 33.1 d	IORE	Non-persistent	PMRA 2350160
Anaerobic clay loam sediment (29.6% sand, 33.6% silt, 36.8% clay, 4.4% organic matter, pH 6.6, CEC 22.2 meq/100 g) 25°C, 183 days	Whole system : 6.7 d	Whole system : 50 d	DFOP	Non-persistent	PMRA 2350160
Aquatic Field studies					
Two aquatic field dissipation studies using zeta-cypermethrin on rice plots in California and Louisiana	The reported half-lives of 181 days in Sutter County, CA, and 126 days in St. Landry Parish, LA, do not agree with the values of the aerobic aquatic biotransformation study (t_2=7 days) or the anaerobic aquatic biotransformation study (t_2=6.7 days). The reported half-lives included the sediments only, not the floodwater.				PMRA 2350160
Crossland (1982) studied the effects of deliberately overspraying ponds with cypermethrin at the rate of 100 g/ha.	4 h after treatment, the concentration of cypermethrin in the surface was 0.1 mg/litre, but fell to about a tenth of this value in 24 h. By 13 days, the surface concentration had fallen to 0.0007 mg/litre. Concentrations at a depth of 50 cm rose to 0.0023-0.0026 mg/litre 4 h after treatment, and then started to fall. By 13 days after treatment, the concentration had decreased to 0.0009 mg/litre. Residues were also found in the sediment at 0.006 mg/kg by the thirteenth day. The initial concentration in the surface film reached 24 mg/litre. There was a very rapid fall to 50 µg/litre after the first week, and by the third week, none could be detected (limit of determination 1-2 µg/litre). In the subsurface water, (limit of determination 0.1 µg/litre), concentrations reached 1µg/litre shortly after treatment but fell rapidly to about a fifth of this value by the end of the first week. By the end of the fourth week, the concentration was below the limit of determination. Sporadic amounts were found in the sediments, but most had disappeared by the end of the study (16 weeks).				PMRA 2350154
The effects of overspraying ponds or streams adjacent to arable fields in the United Kingdom and of treating	The fields were treated at the rate of 70 g a.i./ha and the French vineyards with mistblowers at the rate of 30-45 g a.i./ha. The concentration of cypermethrin in the surface layer of water (0.06 mm) was between 6 and 20 µg/litre but after 24 h, only one of the 14 surface samples showed any cypermethrin, the concentration in this sample				PMRA 1212159

Process	$T_{1/2}$ or DT_{50}	DT_{90}	Kinetics	Comments	PMRA#
vineyards in France with cypermethrin were studied by Crossland et al. (1978).	being 6 µg/litre. Residues in the subsurface layers reached between 0.01 and 0.07 µg/litre after 5 h but then declined; after 24 h, levels in most samples were below the limit of determination (0.01 µg/litre) with only the occasional sample reaching 0.03 µg/litre. In the French vineyards, deposits on the surface of the water were (0.04 - 0.5 mg/m^2). Concentrations in the surface water were initially between 0.14 and 1 mg/litre falling to 0.02 mg/litre within 3 h. Even in the subsurface samples, concentrations of up to 2 µg/litre were occasionally reached, but they fell rapidly and had generally decreased to 0.1 µg/litre or less within a few hours.				

Table 3 Environmental Toxicity of Cypermethrin

Exposure	Species	Test material	Endpoint value	Toxicity Category	Reference
Terrestrial Invertebrates					
Acute	Earthworm (*Eisenia foetida*)	Cypermethrin technical	14-d LC_{50}>100 mg a.i./kg soil		IPCS 1989 PMRA 2350154
Acute	Honey bee (*Apis mellifera*)	Cypermethrin technical	Contact 48-h LD_{50} - 0.023 µg a.i./bee	Highly toxic	USEPA RED PMRA 2350160
Acute	Honey bee (*Apis mellifera*)	Cypermethrin technical	Oral 48-h LD_{50} - 0.172 µg a.i./bee	Highly toxic	USEPA RED PMRA 2350160
Acute lab	Predatory mite (*Typhlodromus pyri*)	Alpha cypermethrin 100 g/l OESC	LR50 = 0.00204 g a.i./ha		European Commission (2004) PMRA 2361203
	Predatory mite (*Typhlodromus pyri*)	Alpha cypermethrin 150 g/kg WG	LR50 = 0.00154 g a.i./ha		European Commission (2004) PMRA 2361203
	Predatory mite (*Typhlodromus pyri*)	Alpha cypermethrin 100 g/l EC	LR50 = 0.00161 g a.i./ha		European Commission (2004) PMRA 2361203
Acute extended lab	Predatory mite (*Typhlodromus pyri*)	Alpha cypermethrin 100 g/l OESC	LR50 = 0.0626 g a.i./ha. No significant effect on reproduction of up to 0.075 g		European Commission (2004)

Exposure	Species	Test material	Endpoint value	Toxicity Category	Reference
			a.i./ha		PMRA 2361203
	Predatory mite (*Typhlodromus pyri*)	Alpha cypermethrin 100 g/l OESC	15 g a.i./ha, 1 or 2 appl. 87-100% mortality at day 0 to day 28 after 1 or 2 appl.		European Commission (2004) PMRA 2361203
Acute lab	Parasitic wasp (*Aphidius rhopalosiphi*)	Alpha cypermethrin 100 g/l OESC	LR50 = 0.256 g a.i./ha		European Commission (2004) PMRA 2361203
	Parasitic wasp (*Aphidius rhopalosiphi*)	Alpha cypermethrin 150 g/kg WG	LR50 = 0.253 g a.i./ha		European Commission (2004) PMRA 2361203
	Parasitic wasp (*Aphidius rhopalosiphi*)	Alpha cypermethrin 100 g/l EC	LR50 = 0.270 g a.i./ha		European Commission (2004) PMRA 2361203
Acute extended lab	Parasitic wasp (*Aphidius rhopalosiphi*)	Alpha cypermethrin 100 g/l OESC	Harmless at 1.2 g a.i./ha		European Commission (2004) PMRA 2361203
	Parasitic wasp (*Aphidius rhopalosiphi*)	Alpha cypermethrin 100 g/l OESC	LR50 = 0.954 g a.i./ha. No significant effect on reproduction of up to 0.75 g a.i./ha		European Commission (2004) PMRA 2361203
	Parasitic wasp (*Aphidius rhopalosiphi*)	Alpha cypermethrin 150 g/kg WG	No effect on mortality at 0.21 and 1.2 g a.i./ha DAT 0 effects on Reproduction at 0.21 and 1.2 g a.i./ha. DAT 0 No effects on mortality and reproduction at 0.21-30 g a.i./ha DAT 21		European Commission (2004) PMRA 2361203
	Wolf spider (*Pardosa spp.*)	Alpha cypermethrin 150 g/kg WG	Harmless at 0.6 and 0.21 g a.i./ha. Moderately harmful at 1.5 g a.i./ha.		European Commission (2004)

Exposure	Species	Test material	Endpoint value	Toxicity Category	Reference
			Harmful at 30 g a.i./ha.		PMRA 2361203
Acute lab	Ground beetle (*Poecilus cupreus*)	Alpha cypermethrin 100 g/l OESC	Harmless at 1.2 g a.i./ha.		European Commission (2004) PMRA 2361203
Acute extended lab	Ground beetle (*Poecilus cupreus*)	Alpha cypermethrin 150 g/kg WG	LR50 > 30 g a.i./ha. Significant reduction in feeding 7 DAT but no significant reduction 7-14 DAT		European Commission (2004) PMRA 2361203
Acute lab	Rove beetle (*Aleochara bilineata*)	Alpha cypermethrin 100 g/l OESC	Harmless at 0.036 to 0.7 g a.i/ha. Slightly harmful at 1.2 g a.i./ha.		European Commission (2004) PMRA 2361203
Acute extended lab	Rove beetle (*Aleochara bilineata*)	Alpha cypermethrin 100 g/l OESC	Harmless at 1.2 g a.i./ha 0 and 7 DAT		European Commission (2004) PMRA 2361203
	Green lacewing (*Chrysoperla carnea*)	Alpha cypermethrin 100 g/l OESC	LR50 = 0.68 g a.i./ha. No effect on reproduction up to 1 g a.i./ha		European Commission (2004) PMRA 2361203
	Green lacewing (*Chrysoperla carnea*)	Alpha cypermethrin 100 g/l OESC	15 g a.i./ha, 1 or 2 appl. Mortality of 50-79% at day 0 to 42 with 1 or 2 appl.; effects on reproduction in all treatments		European Commission (2004) PMRA 2361203
Birds					
Acute oral	Mallard duck (*Anas platyrhynchos*)	Cypermethrin technical	LD_{50} > 9520 mg a.i./kg bw	Practically non-toxic	USEPA RED PMRA 2350160
	Bobwhite quail (*Colinus virginianus*)	Cypermethrin technical	LD_{50} > 2000 mg a.i./kg bw	Practically non-toxic	USEPA RED PMRA 2350159 2350160
	Domestic fowl (*Gallus*	Cypermethrin technical	LD_{50} = > 2000 mg a.i./kg bw	Practically non-toxic	IPCS 1989 PMRA 2350154

Exposure	Species	Test material	Endpoint value	Toxicity Category	Reference
	domesticus)				
	French partridge (*Allectoris rufa*)	Cypermethrin technical	LD_{50} = > 3000 mg a.i./kg bw	Practically non-toxic	IPCS 1989 PMRA 2350154
Dietary	Bobwhite quail (*Colinus virginianus*)	Cypermethrin technical	LC_{50} >5,290 mg a.i./kg diet	Practically non-toxic	USEPA RED PMRA 2350160
	Mallard duck (*Anas platyrhynchos*)	Cypermethrin technical	5 day LC_{50} >2634 mg a.i./kg diet	Practically non-toxic	USEPA RED PMRA 2350159
Chronic (repro)	Bobwhite quail (*Colinus virginianus*)	Cypermethrin technical	NOAEL = 50 mg a.i./kg diet		PMRA 1171378 USEPA RED 2350159 2350160
	Mallard duck (*Anas platyrhynchos*)	Cypermethrin technical	LOAEL > 50 mg a.i./kg diet		PMRA 1171376 USEPA RED 2350159 2350160
Mammals					
Acute oral	Mice (*Mus musculus*) (♂ and ♀)	Cypermethrin technical	LD_{50} = 88 mg a.i./kg bw	Moderately toxic	PMRA 1203062
Chronic repro	Rat (*Rattus norvegicus*)	Cypermethrin technical	2 generation NOAEL = 5.9 mg a.i./kg body weight/day decreased body weight and decreased body weight gain		PMRA 1789398
Terrestrial Plants					
Seedling emergence		Cypermethrin technical	No data		
Vegetative vigor		Cypermethrin technical	No data		

Exposure	Species	Test material	Endpoint value	Toxicity Category	Reference
Freshwater Invertebrates					
Acute	Waterflea (*Daphnia magna*)	Cypermethrin technical	48-h LC50 = 0.42 µg a.i./L	Very highly toxic	USEPA RED PMRA 2350160
	Waterflea (*Ceriodaphnia dubia*)	Cypermethrin technical	48-h LC50 = 0.23 µg a.i./L	Very highly toxic	Mugni et al. 2013 PMRA 2621336
	Amphipod (*Hyalella azteca*)	Cypermethrin technical	96-h EC50 = 0.0036 µg a.i./L	Very highly toxic	USEPA RED PMRA 2350159
	Amphipod (*Hyalella curvispina*)	Cypermethrin technical	48-h LC50 = 0.07 µg a.i./L	Very highly toxic	Mugni et al. 2013 PMRA 2621336
	Water hog louse (*Asellus spp.*)	Cypermethrin technical	24-h LC50 = 0.2 µg a.i./L	Very highly toxic	PMRA 1182894 IPCS 1989 PMRA 2350154
	Freshwater shrimp (*Gammarus pulex*)	Cypermethrin technical	96-h LC50 = 0.009 µg a.i./L	Very highly toxic	PMRA 1182894
	Freshwater shrimp *Paratya autraliensis*	Cypermethrin technical	96-h LC50 = 0.019 µg a.i./L	Very highly toxic	Mugni et al. 2013 PMRA 2621336
	Mosquito (*Aedes aegypti*)	Cypermethrin technical	24-h LC50 = 1.0 µg a.i./L	Very highly toxic	PMRA 1182894
	Pond snail *Lymnea peregra*	Cypermethrin technical	24-h LC50 = 5.0 µg a.i./L	Very highly toxic	PMRA 1182894
	Chironomid	Cypermethrin	24-h LC50 =	Very highly	PMRA 1182894

Exposure	Species	Test material	Endpoint value	Toxicity Category	Reference
	(*Chaoborus crystallinus*)	technical	0.2 µg a.i./L	toxic	
	Chironomid (*Chironomus thummi*)	Cypermethrin technical	24-h LC50 = 5.0 µg a.i./L	Very highly toxic	PMRA 1182894
	Water mite (*Piona carnea*)	Cypermethrin technical	24-h LC50 = 0.05 µg a.i./L	Very highly toxic	PMRA 1182894
	Water boatman (*Corixa punctata*)	Cypermethrin technical	24-h LC50 = 5.0 µg a.i./L	Very highly toxic	PMRA 1182894
	Insect (*Ranatra filiformis*)	Cypermethrin technical	48-h LC50 = 0.09 µg a.i./L	Very highly toxic	Mugni et al. 2013 PMRA 2621336
	Mayfly nymph *Cloeon dipterum*	Cypermethrin technical	48-h LC50 = 0.6 µg a.i./L	Very highly toxic	PMRA 1182894
	Mayfly nymph *Baetis rhodani*	Cypermethrin technical	48-h LC50 = 0.025 µg a.i./L	Very highly toxic	PMRA 1239762
	Crayfish *Orconectes sp.*	Cypermethrin technical	48-h LC50 = 0.07 µg a.i./L	Very highly toxic	PMRA 1239753
	Crustacean (*Diaptomus forbesi*)	Cypermethrin technical	48-h LC50 = 0.03 µg a.i./L	Very highly toxic	Saha and Kaviraj 2008 PMRA 2621334
	Cladoceran (*Daphnia cucullata*)	Cypermethrin technical	48-h LC50 = 0.05 µg a.i./L	Very highly toxic	Mugni et al. 2013 PMRA 2621336
	Copepod (*Eudiaptomus graciloides*)	Cypermethrin technical	48-h LC50 = 0.03 µg a.i./L	Very highly toxic	Mugni et al. 2013 PMRA 2621336
	Oligochaete	Cypermethrin	48-h LC50 =	Highly toxic	Saha and

Exposure	Species	Test material	Endpoint value	Toxicity Category	Reference
	worm (*Branchiura sowerbyi*)	technical	128.7 µg a.i./L		Kaviraj 2008 PMRA 2621334
	waterflea (*Daphnia magna*)	3-phenoxybenzoic acid	48-h EC50 = 89,000 µg a.i./L	Slightly toxic	USEPA RED PMRA 2350160
Chronic	waterflea (*Daphnia magna*)	Cypermethrin technical	21-d NOEC = 0.04 µg a.i./L		European Commission 2005 PMRA 2361190
Sediment	Chironomid *Chironomus riparius*	Cypermethrin technical	10-day LC_{50} - 67 µg a.i./kg sediment		USEPA RED PMRA 2350160
	Amphipod (*Hyalella azteca*)	Cypermethrin technical	10-day LC_{50} - 3.6 µg a.i./kg sediment Morbidity and growth		USEPA RED PMRA 2350159 2350160
Freshwater Fish					
Acute	Rainbow trout *(Oncorhynchus mykiss)*	Cypermethrin technical	96-h LC50 = 0.39 µg a.i./L	Very highly toxic	USEPA RED PMRA 2350159 2350160
	Brown trout (*Salmo trutta*)	Cypermethrin technical	96-h LC50 = 1.2 µg a.i./L	Very highly toxic	PMRA 1212166
	Bluegill sunfish (*Lepomis macrochirus*)	Cypermethrin technical	96-h LC50 = 1.8 µg a.i./L	Very highly toxic	PMRA 1239772
	Atlantic salmon (*Salmo salar*)	Cypermethrin technical	96-h LC50 = 2.0 µg a.i./L	Very highly toxic	IPCS 1989 PMRA 2350154
	Fathead minnow (*Pimphales promelas*)	Cypermethrin technical	96-h LC50 = 1.2 µg a.i./L	Very highly toxic	PMRA 1254861
	Rudd	Cypermethrin	96-h LC50 =	Very highly	IPCS 1989

Exposure	Species	Test material	Endpoint value	Toxicity Category	Reference
	(*Scardinius erythrophthalmus*)	technical	0.4 µg a.i./L	toxic	PMRA 2350154
	Carp (*Cyprinus carpio*)	Cypermethrin technical	96-h LC50 = 0.9 µg a.i./L	Very highly toxic	IPCS 1989 PMRA 2350154
	Tilapia nilotica	Cypermethrin technical	96-h LC50 = 2.0 µg a.i./L	Very highly toxic	IPCS 1989 PMRA 2350154
	Bluegill sunfish (*Lepomis macrochirus*)	3-phenoxybenzoic acid	96-h LC50 = 36,300 µg a.i./L	Slightly toxic	PMRA 1239733 USEPA RED 2350160
	Rainbow trout *(Oncorhynchus mykiss)*	3-phenoxybenzoic acid	96-h LC50 = 13,300 µg a.i./L	Slightly toxic	PMRA 1160907 1239776 USEPA RED 2350160
	Rainbow trout *(Oncorhynchus mykiss)*	Cis/trans DCVA	96-h LC50 = 3,100 µg a.i./L	Slightly toxic	PMRA 1160907
Chronic	Fathead minnow (*Pimphales promelas*)	Cypermethrin technical	30-d NOAEC = 0.14 µg a.i./L LOAEC = 0.33µg a.i./L Growth and mortality		USEPA RED PMRA 2350159 2350160
Aquatic Plants					
Acute	Duckweed (*Lemna gibba*)	Alpha cypermethrin	96-h EC50 > 1.39 µg a.i./L NOAEC = 1.39 µg a.i./L		USEPA alpha cypermethrin PMRA 2621333
	Algae (*Selenastrum capricornutum*)	Cypermethrin technical	96-h EC50 > 100 µg a.i./L		European Commission 2005 PMRA 2361190

Exposure	Species	Test material	Endpoint value	Toxicity Category	Reference
Amphibians					
Acute	Tadpole larvae (*Bufo melanostictus*)	Cypermethrin technical	96-h LC50 = 9 µg a.i./L	Very highly toxic	Saha and Kaviraj 2008 PMRA 2621334
	Tadpole larvae (*Hypsiboas pulchellus*)	Cypermethrin technical	96-h LC50 = 480 µg a.i./L	Highly toxic	Agostini et al. 2010 PMRA 2621335
Estuarine/Marine Invertebrates					
Acute	Mysid shrimp (*Mysidopsis bahia*)	Cypermethrin technical	96-h LC50 = 0.00475 µg a.i./L	Very highly toxic	PMRA 1239756 USEPA RED 2350159 2350160
	Sand shrimp (*Crangon septemspinosa*)	Cypermethrin technical	96-h LC50 = 0.01 µg a.i./L	Very highly toxic	IPCS 1989 PMRA 2350154
	Grass shrimp (*Palaemonetes pugio*)	Cypermethrin technical	96-h LC50 = 0.016 µg a.i./L	Very highly toxic	Mugni et al. 2013 PMRA 2621336
	Pink shrimp (*Penaeus duorarum*)	Cypermethrin technical	96-h LC50 = 0.036 µg a.i./L	Very highly toxic	PMRA 1239755
	Copepod (*Oithona similis*)	Cypermethrin technical	48-h LC50 = 0.24 µg a.i./L	Very highly toxic	Mugni et al. 2013 PMRA 2621336
	Lobster (*Homarus americanus*)	Cypermethrin technical	96-h LC50 = 0.04 µg a.i./L	Very highly toxic	USEPA RED PMRA 2350160
	Fiddler crab (*Uca sp.*)	Cypermethrin technical	96-h LC50 = 0.197 µg a.i./L	Very highly toxic	USEPA RED PMRA 2350160
	Eastern oyster (*Crassostrea*	Cypermethrin technical	96-h EC50 = 370 µg a.i./L	Highly toxic	PMRA 1239763 USEPA RED

Exposure	Species	Test material	Endpoint value	Toxicity Category	Reference
	virginica)				PMRA 2350160
Chronic	Mysid shrimp (*Mysidopsis bahia*)	Cypermethrin technical	28-d NOAEC = 0.000781 µg a.i./L LOAEC = 0.00197 µg a.i./L weight of females reduced	Very highly toxic	USEPA RED PMRA 2350159 2350160
Estuarine/Marine Fish					
Acute	Sheepshead minnow (*Cyprinidon variegates*)	Cypermethrin technical	96-h LC50 = 0.95 µg a.i./L	Very highly toxic	PMRA 1239773 USEPA RED PMRA 2350159 2350160
	Atlantic salmon (*Salmo salar*)	Cypermethrin technical	96-h LC50 = 4.3 µg a.i./L	Very highly toxic	USEPA RED PMRA 2350160
	Sheepshead minnow (*Cyprinidon variegates*)	Cis/trans DCVA	96-h LC50 = 3000 µg a.i./L	Slightly toxic	PMRA 1160907
Aquatic Plants					
Acute	*Skeletonema costatum*	Alpha cypermethrin	96-h EC50 > 33.5 µg a.i./L NOAEC = 33.5 µg a.i./L		USEPA alpha cypermethrin PMRA 2621333

Table 4 Risk of cypermethrin to terrestrial organisms other than birds and mammals

Organism	Exposure	Endpoint value	EEC	RQ	Level of concern
Invertebrates					
Earthworm	Acute	$LC_{50}/2$ = >50 mg a.i./kg soil	0.12 mg a.i./kg dw soil (apples)	<0.002	Not exceeded
Bee	Oral	48h-LD_{50} = 0.172 µg a.i./bee	0.827 µg a.i./bee (sunflower)	4.8	Exceeded
	Contact	48h-LD_{50} = 0.023 µg a.i./bee	0.068 µg a.i./bee (sunflower)	2.95	Exceeded

Organism	Exposure	Endpoint value	EEC	RQ	Level of concern
Predatory mite (*Typhlodromus pyri*)	Acute	LR_{50} = 0.00154 g a.i./ha	In-field : 28.5 g a.i./ha (sunflowers)	In-field: (sunflowers) 18 507	Exceeded
			Off-field : 7.4 g a.i./ha (sunflowers)	Off-field: (sunflowers) 4805	Exceeded
Parasitic wasp (*Aphidius rhopalosiphi*)	Acute	LR_{50} = 0.253 g a.i./ha	In-field : 28.5 g a.i./ha (sunflowers)	In-field: (sunflowers) 113	Exceeded
			Off-field : 7.4 g a.i./ha (sunflowers)	Off-field: (sunflowers) 29	Exceeded
Vascular plants					
Vascular plant	Seedling emergence	No data available			
	Vegetative vigour	No data available			

Table 5 Refined risk assessments of cypermethrin for terrestrial non-target arthropods

Organism	Exposure	Endpoint value	EEC	RQ	Level of concern
Predatory mite (*Typhlodromus pyri*)	Extended laboratory	LR_{50} = 0.0626 g a.i./ha	In-field: 25.7 g a.i./ha	In-field: 411	Exceeded
			Off field: 0.74 g a.i./ha	Off-field: 11.8	Exceeded
A. rhopalosiphi (aphid parasitoid) foliar dwelling parasite	Extended laboratory	LR_{50} = 0.954 g a.i./ha	In-field: 25.7 g a.i./ha	In-field: 27	Exceeded
			Off-field: 0.74 g a.i./ha	Off-field: 0.8	Not exceeded

Table 6 Expanded screening level risk assessment of cypermethrin for birds based on the highest seasonal airblast application on apples (101.8 g a.i./ha × 3 at 7 day interval).

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues	
			On-field		Off-field		On-field	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Small Bird (0.02 kg)								
Reproduction	>5.3	Insectivore (small insects)	10.23	**<1.93**	7.57	**<1.43**	5.71	**<1.08**
	>5.3	Granivore (grain and seeds)	2.56	<0.48	1.89	<0.36	1.22	<0.23
	>5.3	Frugivore (fruit)	5.12	<0.97	3.79	<0.71	2.44	<0.46

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues	
			On-field		Off-field		On-field	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Medium-Sized Bird (0.1 kg)								
Reproduction	>5.3	Insectivore (small insects)	7.98	**<1.51**	5.91	**<1.11**	4.45	<0.84
	>5.3	Insectivore (large insects)	2.00	<0.38	1.48	<0.28	0.95	<0.18
	>5.3	Granivore (grain and seeds)	2.00	<0.38	1.48	<0.28	0.95	<0.18
	>5.3	Frugivore (fruit)	3.99	<0.75	2.95	<0.56	1.90	<0.36
Large-Sized Bird (1 kg)								
Reproduction	>5.3	Insectivore (small insects)	2.33	<0.44	1.73	<0.33	1.30	<0.25
	>5.3	Insectivore (large insects)	0.58	<0.11	0.43	<0.08	0.28	<0.05
	>5.3	Granivore (grain and seeds)	0.58	<0.11	0.43	<0.08	0.28	<0.05
	>5.3	Frugivore (fruit)	1.17	<0.22	0.86	<0.16	0.56	<0.10
	>5.3	Herbivore (short grass)	8.33	**<1.57**	6.17	**<1.16**	2.96	<0.56
	>5.3	Herbivore (long grass)	5.09	<0.96	3.76	<0.71	1.66	<0.31
	>5.3	Herbivore (forage crops)	7.71	**<1.45**	5.70	**<1.08**	2.55	<0.48

Table 7 Expanded screening level risk assessment of cypermethrin for wild mammals based on the highest seasonal airblast application on apples (101.8 g a.i./ha × 3 at 7 day interval).

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues	
			On-field		Off-Field		On-field	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Medium-Sized Mammal (0.035 kg)								
Acute	8.80	Insectivore (small insects)	5.16	0.58	3.82	0.43	2.88	0.33
	8.80	Insectivore (large insects)	1.29	0.15	0.95	0.11	0.62	0.07
	8.80	Granivore (grain and seeds)	1.29	0.15	0.95	0.11	0.62	0.07
	8.80	Frugivore (fruit)	2.58	0.29	1.91	0.20	1.23	0.14
	8.80	Herbivore (short grass)	18.44	**2.1**	13.64	**1.6**	6.55	0.74
	8.80	Herbivore (long grass)	11.26	**1.3**	8.33	0.95	3.68	0.42
	8.80	Herbivore (forage crops)	17.06	**1.9**	12.62	**1.4**	5.64	0.64
Reproduction	5.90	Insectivore (small insects)	5.16	0.9	3.82	0.65	2.88	0.49
	5.90	Insectivore (large insects)	1.29	0.2	0.95	0.16	0.62	0.10
	5.90	Granivore (grain and seeds)	1.29	0.2	0.95	0.16	0.62	0.10
	5.90	Frugivore (fruit)	2.58	0.4	1.91	0.32	1.23	0.21
	5.90	Herbivore (short grass)	18.44	**3.1**	13.64	**2.3**	6.55	**1.11**
	5.90	Herbivore (long grass)	11.26	**1.9**	8.33	**1.4**	3.68	0.62
	5.90	Herbivore (forage crops)	17.06	**2.9**	12.62	**2.1**	5.64	0.96

	Toxicity (mg a.i./kg bw/d)	Food Guild (food item)	Maximum nomogram residues				Mean nomogram residues	
			On-field		Off-Field		On-field	
			EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ	EDE (mg a.i./kg bw)	RQ
Large-Sized Mammal (1 kg)								
Acute	8.80	Insectivore (small insects)	2.76	0.3	2.04	0.23	1.54	0.17
	8.80	Insectivore (large insects)	0.69	0.08	0.51	0.06	0.33	0.04
	8.80	Granivore (grain and seeds)	0.69	0.08	0.51	0.06	0.33	0.04
	8.80	Frugivore (fruit)	1.38	0.2	1.02	0.11	0.66	0.07
	8.80	Herbivore (short grass)	9.85	**1.1**	7.29	0.83	3.50	0.40
	8.80	Herbivore (long grass)	6.02	0.7	4.45	0.51	1.96	0.22
	8.80	Herbivore (forage crops)	9.11	**1.0**	6.74	0.77	01	0.34
Reproduction	5.90	Insectivore (small insects)	2.76	0.5	2.04	0.35	1.54	0.26
	5.90	Insectivore (large insects)	0.69	0.1	0.51	0.09	0.33	0.06
	5.90	Granivore (grain and seeds)	0.69	0.1	0.51	0.09	0.33	0.06
	5.90	Frugivore (fruit)	1.38	0.2	1.02	0.17	0.66	0.11
	5.90	Herbivore (short grass)	9.85	**1.7**	7.29	**1.24**	3.50	0.59
	5.90	Herbivore (long grass)	6.02	**1.0**	4.45	0.75	1.96	0.33
	5.90	Herbivore (forage crops)	9.11	**1.5**	6.74	**1.14**	3.01	0.51

Table 8 Refined Risk Assessment for Aquatic Organisms (Off-field, spray drift)

Organism	Exposure	Endpoint value[1]	Application rate	RQ		
				11%	74%	26%
Freshwater Species						
Invertebrates	Acute	HC_5 from SSD (0.003 µg a.i./L)	101.8 g a.i./ha × 3		**5333.3**	
			71.0 g a.i./ha × 3	**666.7**		
			71.0 g a.i./ha × 2		**3333.3**	**1000**
			28.5 g a.i./ha × 2	**200.0**		
			28.5 g a.i./ha × 1			**333.3**
Waterflea (*Daphnia magna*)	Chronic	21-d NOEC (0.04 µg a.i./L)	101.8 g a.i./ha × 3		**400.0**	
			71.0 g a.i./ha × 3	**50.0**		
			71.0 g a.i./ha × 2		**250.0**	**75.0**
			28.5 g a.i./ha × 2	**15.0**		
			28.5 g a.i./ha × 1			**25.0**
Fish	Acute	HC_5 from SSD (0.33 µg a.i./L)	101.8 g a.i./ha × 3		**48.5**	
			71.0 g a.i./ha × 3	**6.1**		
			71.0 g a.i./ha × 2		**30.3**	**9.1**
			28.5 g a.i./ha × 2	**1.8**		
			28.5 g a.i./ha × 1			**3.0**
Fathead minnow (*Pimphales promelas*)	Chronic	30-d NOEC (0.14 µg a.i./L)	101.8 g a.i./ha × 3		**114.3**	
			71.0 g a.i./ha × 3	**14.3**		
			71.0 g a.i./ha × 2		**71.4**	**21.4**
			28.5 g a.i./ha × 2	**4.3**		
			28.5 g a.i./ha × 1			**7.1**

Organism	Exposure	Endpoint value[1]	Application rate	RQ		
				11%	74%	26%
Aquatic plant Duckweed (*Lemna gibba*)	Acute	96-h EC50 ÷ 2 (>0.7 µg a.i./L)	101.8 g a.i./ha × 3		**<22.9**	
			71.0 g a.i./ha × 3	**<3.0**		
			71.0 g a.i./ha × 2		**<14.3**	**<4.3**
			28.5 g a.i./ha × 2	**<1.0**		
			28.5 g a.i./ha × 1			**<1.4**
Amphibians (*Bufo melanostictus*)	Acute	96-h LC_{50} ÷ 10 (0.9 µg a.i./L)	101.8 g a.i./ha × 3		**97.8**	
			71.0 g a.i./ha × 3	**10.0**		
			71.0 g a.i./ha × 2		**58.9**	**21.1**
			28.5 g a.i./ha × 2	**3.3**		
			28.5 g a.i./ha × 1			**5.6**
Amphibians[2]	Chronic	30-d NOEC (0.14 µg a.i./L)	101.8 g a.i./ha × 3		**628.6**	
			71.0 g a.i./ha × 3	**64.3**		
			71.0 g a.i./ha × 2		**378.6**	**135.7**
			28.5 g a.i./ha × 2	**21.4**		
			28.5 g a.i./ha × 1			**35.7**
Marine/Estuarine Species						
Estuarine/marine invertebrates	Acute	HC_5 from SSD (0.0004 µg a.i./L)	101.8 g a.i./ha × 3		**40 000.0**	
			71.0 g a.i./ha × 3	**5000**		
			71.0 g a.i./ha × 2		**25 000**	**7500.0**
			28.5 g a.i./ha × 2	**1500**		
			28.5 g a.i./ha × 1			**2500.0**
Mysid shrimp (*Mysidopsis bahia*)	Chronic	28-d NOAEC (0.0008 µg a.i./L)	101.8 g a.i./ha × 3		**20 000.0**	
			71.0 g a.i./ha × 3	**2500**		
			71.0 g a.i./ha × 2		**12 500.0**	**3750.0**
			28.5 g a.i./ha × 2	**750**		
			28.5 g a.i./ha × 1			**1250.0**
Fish (*Cyprinidon variegates*)	Acute	96-h LC_{50} ÷ 10 (0.095 µg a.i./L)	101.8 g a.i./ha × 3		**168.4**	
			71.0 g a.i./ha × 3	**21.1**		
			71.0 g a.i./ha × 2		**105.3**	**31.6**
			28.5 g a.i./ha × 2	**6.3**		
			28.5 g a.i./ha × 1			**10.5**
Algae (*Skeletonema costatum*)	Chronic	96-h EC50 ÷ 2 (>16.8 µg a.i./L)	101.8 g a.i./ha × 3		<0.95	
			71.0 g a.i./ha × 3	<0.12		
			71.0 g a.i./ha × 2		<0.6	<0.18
			28.5 g a.i./ha × 2	<0.04		
			28.5 g a.i./ha × 1			<0.06

[1] Endpoints were divided by an Uncertainty Factor to account for varying protection goals (that is, protection at the community, population, or individual level)
[2] Endpoints from fish used as surrogate

Values in bold exceed Level of concern (≥ 1)

Table 9 Refined Risk Assessment for Aquatic Organisms (Runoff)

Organism	Endpoint value[1]	Scenario	EEC (µg a.i./L)[2]	RQ	LOC Exceeded
Freshwater Species					
Invertebrates	Acute HC_5 from SSD (0.003 µg a.i./L)	Apples	0.16	**53.3**	Yes
		Potatoes	0.99	**330.0**	Yes
		Sunflowers	0.18	**60.0**	Yes

Organism	Endpoint value[1]	Scenario	EEC (µg a.i./L)[2]	RQ	LOC Exceeded
Waterflea (*Daphnia magna*)	Chronic 21-d NOEC (0.04 µg a.i./L)	Apples	0.006	0.15	No
		Potatoes	0.058	**1.5**	Yes
		Sunflowers	0.009	0.2	No
Fish	Acute HC_5 from SSD (0.33 µg a.i./L)	Apples	0.16	0.5	No
		Potatoes	0.99	**3.0**	Yes
		Sunflowers	0.18	0.6	No
Fathead minnow (*Pimphales promelas*)	Chronic 30-d NOEC (0.14 µg a.i./L)	Apples	0.006	0.04	No
		Potatoes	0.058	0.4	No
		Sunflowers	0.009	0.06	No
Aquatic plant Duckweed (*Lemna gibba*)	Acute 96-h EC50 ÷ 2 (>0.7 µg a.i./L)	Apples	0.16	<0.2	No
		Potatoes	0.99	**<1.4**	Yes
		Sunflowers	0.18	<0.3	No
Amphibians (*Bufo melanostictus*)	Acute 96-h LC_{50} ÷ 10 (0.9 µg a.i./L)	Apples	0.85	0.9	No
		Potatoes	5.3	**5.9**	Yes
		Sunflowers	0.97	**1.1**	Yes
Amphibians[3]	Chronic 30-d NOEC (0.14 µg a.i./L)	Apples	0.024	0.2	No
		Potatoes	0.23	**1.6**	Yes
		Sunflowers	0.034	0.2	No
Estuarine/Marine Species					
Estuarine/marine invertebrates	Acute HC_5 from SSD (0.0004 µg a.i./L)	Apples	0.16	**400.0**	Yes
		Potatoes	0.99	**2475.0**	Yes
		Sunflowers	0.18	**450.0**	Yes
Mysid shrimp (*Mysidopsis bahia*)	Chronic 28-d NOAEC (0.0008 µg a.i./L)				
		Apples	0.006	**7.5**	Yes
		Potatoes	0.058	**72.5**	Yes
		Sunflowers	0.009	**11.3**	Yes
Fish (*Cyprinidon variegates*)	Acute 96-h LC_{50} ÷ 10 (0.095 µg a.i./L)	Apples	0.16	**1.7**	Yes
		Potatoes	0.99	**10.4**	Yes
		Sunflowers	0.18	**1.9**	Yes

Organism	Endpoint value[1]	Scenario	EEC (µg a.i./L)[2]	RQ	LOC Exceeded
Algae (*Skeletonema costatum*)	Chronic 96-h EC50 ÷ 2 (>16.8 µg a.i./L)	Apples	0.16	<0.01	No
		Potatoes	0.99	<0.06	No
		Sunflowers	0.18	<0.01	No

[1)] Endpoints were divided by an Uncertainty Factor to account for varying protection goals (that is, protection at the community, population, or individual level)
[2)] EEC based on a 15 cm water body depth for amphibians and a 80 cm water depth for all other aquatic organisms.
[3)] Endpoints from fish used as surrogate

Values in bold exceed Level of concern (≥ 1)

Table 10 Risk to Aquatic Organisms from concentrations of cypermethrin in surface water from Canadian monitoring data

Organism	Endpoint value[1]	Scenario	EEC (µg a.i./L)[2]	RQ	LOC Exceeded
Freshwater Species					
Invertebrates	Acute HC_5 from SSD (0.003 µg a.i./L)	Surface water from Prince Edward Island	9.44	**3146.7**	Yes
Fish	Acute HC_5 from SSD (0.33 µg a.i./L)	Surface water from Prince Edward Island	9.44	**28.6**	Yes
Aquatic plant Duckweed (*Lemna gibba*)	Acute 96-h EC50 ÷ 2 (>0.7 µg a.i./L)	Surface water from Prince Edward Island	9.44	**<13.5**	Yes
Algae (*Selenastrum capricornutum*)	Chronic 96-h EC50 ÷ 2 (>50 µg a.i./L)	Surface water from Prince Edward Island	9.44	<0.19	No
Amphibians (*Bufo melanostictus*)	Acute 96-h LC_{50} ÷ 10 (0.9 µg a.i./L)	Surface water from Prince Edward Island	9.44	**10.5**	Yes
Estuarine/Marine Species					
Estuarine/marine invertebrates	Acute HC_5 from SSD (0.0004 µg a.i./L)	Surface water from Prince Edward Island	9.44	**23 600.0**	Yes
Fish (*Cyprinidon variegates*)	Acute 96-h LC_{50} ÷ 10 (0.095 µg a.i./L)	Surface water from Prince Edward Island	9.44	**99.4**	Yes
Algae (*Skeletonema costatum*)	Chronic 96-h EC50 ÷ 2 (>16.8 µg a.i./L)	Surface water from Prince Edward Island	9.44	<0.6	No

[1)] Endpoints were divided by an Uncertainty Factor to account for varying protection goals (that is, protection at the community, population, or individual level)
[2)] Maximum concentration observed in surface water from Canadian monitoring data

Values in bold exceed Level of concern (≥ 1)

Table 11 Level 1 aquatic ecoscenario modelling EECs (Φg a.i./L) in water column for cypermethrin in a water body 0.8 m deep, excluding spray drift

Crop-region	EEC (Φg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Apples-BC	0.016	0.002	<0.001	<0.001	<0.001	<0.001
Apples-ON	0.091	0.013	0.004	0.002	0.002	<0.001
Apples-QC	0.098	0.014	0.004	0.002	0.001	<0.001
Apples-NS	0.16	0.023	0.006	0.004	0.003	0.001
Maximum for apple use	**0.16**	**0.023**	**0.006**	**0.004**	**0.003**	**0.001**
Potatoes-MB	0.92	0.14	0.045	0.028	0.022	0.008
Potatoes-ON	0.31	0.055	0.017	0.011	0.010	0.005
Potatoes-QC	0.58	0.086	0.029	0.018	0.015	0.009
Potatoes-PEI	0.99	0.16	0.058	0.034	0.029	0.015
Maximum for potato use	**0.99**	**0.16**	**0.058**	**0.034**	**0.029**	**0.015**
Sunflowers-MB	0.18	0.027	0.009	0.006	0.004	0.002
Sunflowers-ON	0.062	0.010	0.004	0.002	0.002	<0.001
Sunflowers-QC	0.11	0.017	0.005	0.003	0.003	0.002
Maximum for sunflower use	**0.18**	**0.027**	**0.009**	**0.006**	**0.004**	**0.002**

Table 12 Level 1 aquatic ecoscenario modelling EECs (Φg a.i./L) in water column for cypermethrin in a water body 0.15 m deep, excluding spray drift

Crop-region	EEC (Φg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Apples-BC	0.083	0.010	0.002	<0.001	<0.001	<0.001
Apples-ON	0.49	0.062	0.014	0.007	0.005	0.002
Apples-QC	0.52	0.066	0.016	0.006	0.005	0.002
Apples-NS	0.85	0.11	0.024	0.011	0.009	0.003
Maximum for apple use	**0.85**	**0.11**	**0.024**	**0.011**	**0.009**	**0.003**
Potatoes-MB	4.8*	0.67	0.17	0.088	0.066	0.021
Potatoes-ON	1.7	0.25	0.065	0.033	0.028	0.012
Potatoes-QC	3.1	0.40	0.10	0.050	0.041	0.020
Potatoes-PEI	5.3*	0.75	0.23	0.11	0.086	0.035
Maximum for potato use	**5.3***	**0.75**	**0.23**	**0.11**	**0.086**	**0.035**
Sunflowers-MB	0.97	0.13	0.034	0.017	0.013	0.004
Sunflowers-ON	0.33	0.047	0.014	0.006	0.005	0.002

Crop-region	EEC (Φg a.i./L)					
	Peak	96-hour	21-day	60-day	90-day	Yearly
Sunflowers-QC	0.59	0.076	0.020	0.010	0.008	0.004
Maximum for sunflower use	**0.97**	**0.13**	**0.034**	**0.017**	**0.013**	**0.004**

*note – limit of solubility is 4 (Φg a.i./L) in buffered pH 7 water.

Table 13 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Cypermethrin Are criteria met?
CEPA toxic or CEPA toxic equivalent[1]	Yes		Yes
Predominantly anthropogenic[2]	Yes		Yes
Persistence[3]:	Soil	Half-life ≥ 182 days	No: 20-61 days
	Water	Half-life ≥ 182 days	No: 7 days
	Sediment	Half-life ≥ 365 days	No: 6.7-181 days
	Air	Half-life ≥ 2 days or evidence of long range transport	Volatilization is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (2.5×10^{-9} mm/Hg) and Henry's Law Constant (3.4×10^{-7} atm m^3/mole).
Bioaccumulation[4]	Log $K_{OW} \geq 5$		Yes: 6.5
	BCF ≥ 5000		No: 3.5-1200
	BAF ≥ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			**No, does not meet all TSMP Track 1 criteria.**

[1]All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (that is, all other TSMP criteria are met).
[2]The policy considers a substance "predominantly anthropogenic" if, based on expert judgment, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.
[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.
[4]The log L_{OW} and/or BCF and/or BAF are preferred over log K_{OW}.

Appendix VII Water Monitoring Data

Canadian data are available from agricultural areas in several provinces where cypermethrin is currently registered for use. Sampling generally occurred between May and October, and was occasionally done during precipitation events. Large data sets were available from across the United States, where sampling occurred throughout the year. The majority of the monitoring data available from Canada and the United States may not have been targeted to capture absolute peak surface water concentrations. Generally, the surface water and groundwater data available for cypermethrin are considered relevant.

Overall, cypermethrin was detected in < 3% (17 out of 605) of groundwater samples and in < 1% (12 out of 1213) of surface water samples analyzed in the relevant agricultural areas of Canada. The highest concentrations of cypermethrin detected were in Prince Edward Island (1.66 µg/L in groundwater and 9.44 µg/L in surface water). Data from United States are very similar to the Canadian data. There were no detections of cypermethrin in 8,235 groundwater and treated water samples analyzed in the US, which included agricultural areas. Detections in surface water were <1% (11 out of 12,528 samples analyzed).

Cypermethrin detections in Prince Edward Island surface water, as high as 9.44 µg/L, were likely a result of run-off following precipitation events. Five of the samples collected exceeded the limit of solubility of 4 µg/L. As noted above, sampling occurred mainly after rainfall events and the detections were limited to two dates at all sites. Cypermethrin is highly insoluble in water (limit of solubility of 4 µg/L in pH 7 buffered water) and binds strongly to organic material (Koc value of 20 800 ml/g – the smallest of 4 Kfoc values). Cypermethrin may reach surface water through run-off while sorbed onto soil particles. It is not expected to persist in surface waters; based on its characteristics, it is expected to partition readily to sediment. Factors that can influence cypermethrin's solubility in water include pH, organic matter, particulate matter, temperature, etc., resulting in levels in ambient water that are higher than the limit of solubility for pH 7 buffered water.

Appendix VIII Proposed Label Amendments for Products Containing Cypermethrin

The label amendments presented below do not include all label requirements for individual products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the following label statements.

I) The following changes are proposed to the labels of technical class products containing cypermethrin:

1) The following statement is proposed to be added to the labels of technical grade cypermethrin under the section entitled "Toxicological Information":

   "Skin exposure may cause transient sensations (tingling, burning, itching, numbness). Treat symptomatically."

2) The following statement is proposed to be added to the "Environmental Hazards" section of the Cypermethrin Technical Insecticide label:

   "TOXIC to aquatic organisms."

3) The following statement is proposed to be added under the "Precautions" Section of the Cypermethrin Technical Insecticide label:

   "DO NOT discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters."

II) The following changes are proposed to the labels of commercial class products containing cypermethrin:

1) The following label statement is proposed to be added to commercial end-use product labels:

   "Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings."

2) The following statement is proposed to be added to the labels of commercial class products containing cypermethrin under the section entitled "Toxicological Information":

   "Skin exposure may cause transient sensations (tingling, burning, itching, numbness). Treat symptomatically."

3) The following statements are proposed to be added to the "Environmental Hazards" section of all product labels:

"Toxic to aquatic organisms. Observe buffer zones specified under DIRECTIONS FOR USE."

"Toxic to bees. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site. Avoid application during the crop blooming period. If applications must be made during the crop blooming period, restrict applications to the early morning or the evening when most bees are not foraging. Avoid applications when bees are foraging in the treatment area in ground cover containing blooming weeds. To further minimize exposure to pollinators, refer to the complete guidance "Protecting Pollinators during Pesticide Spraying – Best Management Practices" on the Health Canada website (www.healthcanada.gc.ca/pollinators)."

"Toxic to certain beneficial insects. Minimize spray drift to reduce harmful effects on beneficial insects in habitats next to the application site such as hedgerows and woodland."

"To reduce run-off from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay."

"Avoid application of this product when heavy rain is forecast."

"Contamination of aquatic areas as a result of run-off may be reduced by including a vegetative strip between the treated area and the edge of the water body."

4) The following statements are proposed to be added to the "Directions for Use" Section on all product labels:

"As this product is not registered for the control of pests in aquatic systems, DO NOT use to control aquatic pests."

"DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes."

"Field sprayer application: DO NOT apply during periods of dead calm. Avoid application of this product when winds are gusty. DO NOT apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) fine classification. Boom height must be 60 cm or less above the crop or ground.

Airblast application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** direct spray above plants to be treated. Turn off outward pointing nozzles at row ends and outer rows. **DO NOT** apply when wind speed is greater than 16 km/h at the application site as measured outside of the treatment. area on the upwind side.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 8 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE S572.1) coarse

classification. To reduce drift caused by turbulent wingtip vortices, the nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing- or rotorspan."

"**Buffer zones:**

Use of the following spray methods or equipment **DO NOT** require a buffer zone: hand-held or backpack sprayer and spot treatment.

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive freshwater habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs and wetlands) and estuarine/marine habitats.

Method of application	Crop		Buffer Zones (metres) Required for the Protection of:			
			Freshwater Habitat of Depths:		Estuarine/Marine Habitats of Depths:	
			Less than1 m	Greater than 1 m	Less than 1 m	Greater than 1 m
Field sprayer	Tobacco		60	25	120	120
	Conifer seedling, canola, evening primrose, corn, carrot, lettuce, onions, strawberry, tobacco seedlings		50	25	120	120
	Potato, stevia		45	20	120	115
	Cole crops, rutabaga, turnip		40	20	120	100
	Asparagus, tomato		30	15	120	75
	Barley, wheat		30	15	120	80
	Roadsides, summer fallow		25	10	120	60
	Sunflower		20	10	115	55
Airblast	Apple, pear	Early growth stage	75	65	95	85
	Grape, peach	Early growth stage	70	60	90	80
Aerial	Corn	Fixed wing	800	550	800	800
		Rotary wing	700	400	800	800
	Canola	Fixed wing	625	350	800	800
		Rotary wing	425	200	800	800
	Sunflower	Fixed wing	600	325	800	800
		Rotary wing	325	175	800	800
	Potato	Fixed wing	800	800	800	800
		Rotary wing	675	350	800	800

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

The buffer zones for this product can be modified based on weather conditions and spray equipment configuration by accessing the Buffer Zone Calculator on the Pest Management Regulatory Agency portion of the Health Canada web site. Buffer zones of 120 m (field sprayer) or 800 m (aerial sprayer) CANNOT be modified."

5) The following statements are proposed to be added to the "Directions for Use" Section for the following crops:

- For Stevia: "Use a minimum of 100 litres and no more than 500 litres of spray solution per hectare."
- For greenhouse Tobacco Seedlings: "Do not apply by fogger or hand-held mistblower."
- For Lettuce and Tomato: "NOT FOR GREENHOUSE USE"
- For all crops: "Crop Rotation: Rotational crops may not be planted within 30 days after the last application, except crops on which cypermethrin is registered (listed on this label)."

6) In order for use directions of products containing cypermethrin to be consistent with the assumptions used in the PMRA risk assessment, the information highlighted in grey in the table below is proposed to be specified on cypermethrin labels, where applicable:

Site/Crop	Spray Volume (Litres/ha)	Maximum Number of Applications	Minimum Interval between Applications (days)
Conifer seedling (Nursery)	100-500	3	7
Roadsides	110	3	7
Summer fallow, headlands	110	3	7
Barley	110	3	7
	200-500	1	N/A
Wheat	110	3	7
	200-500	1	N/A
Canola	100-500	3	7
Sunflower	100-120	2	5
Corn	300-500	3	7
Corn – seedlings	200-500	1	N/A
Apples	3333 for dilute sprays	3	7
Potato	200-500	2	10
	100-500	3	10
Asparagus	100-500	3	7
Carrot	550	3	7
Carrot (seedlings)	200-500	3	7
Celery	500	3	7
Cole crops (such as cabbage, cauliflower, broccoli and Brussels sprouts)	100-500	3	14

Site/Crop	Spray Volume (Litres/ha)	Maximum Number of Applications	Minimum Interval between Applications (days)
Cole crops (such as cabbage, cauliflower, broccoli and Brussels sprouts) – seedlings	200-500	1	N/A
Lettuce	100-500	4	7
	200-500	3	7
Grape (excluding table grapes) – Hand harvest	400 or more	2	7
Grape (excluding table grapes) – Mechanical harvest	400 or more	3	7
Grapes	100-500	3	7
Onions	100-500	3	7
Onions (seedlings and transplants)	200-500	1	N/A
Peach	550 for airblast sprayer 3333 for dilute sprays	2	7
Nectarine	550 for airblast sprayer 3333 for dilute sprays	2	7
Pear	3333 for dilute sprays	2	7
	500-1500	3	7
Plum	500-1500	3	7
Rutabaga, Turnip	100-500	3	7
Strawberry	300-500	3	7
	100-500	2	7
	100-500	3	7
Tomato	100-500	3	7
Tobacco – Post-plant treatment	150-300	2	7

7) The following statement is proposed to be added to the "PROTECTIVE CLOTHING AND EQUIPMENT" section:

For Mechanically Pressurized Handgun application to strawberry: Wear coveralls (over single layer of clothes) and chemical-resistant gloves during mixing, loading and application."

8) Proposed restricted entry intervals (REI) are specified in the following table.

Crop	Postapplication Activity	Proposed REI
Corn, Sweet	Hand harvesting	5 days
	All other activities	12 hours
Grape	Girdling	7 days
	Turning	7 days

	All other activities	12 hours
All other crops	All activities	12 hours

9) The changes are proposed to the "PRECAUTIONARY STATEMENTS" sections of the products noted below:

For Up-Cyde 2.5 EC Agricultural (Reg. No. 28795):

Remove: "In addition, wear a face shield or eye goggles when mixing."

Replace with: "In addition, wear goggles or face shield during mixing and loading."

For Ripcord 400 EC Agricultural Insecticide (Reg. No. 15738) and Ripcord Insecticide (Reg. No. 30316):

Remove: "Wear long-sleeved protective clothing and gloves when handling or applying material. Wear face shield or eye goggles when mixing."

Replace with: "Wear long-sleeved shirt, long pants and chemical-resistant gloves during mixing, loading, application, clean up and repair. In addition, wear goggles or face shield during mixing and loading."

References

A. Information considered in the Chemistry Assessment

Pest Control Products Act Registration Number 19186

PMRA Document Number	Reference
1636418	[Privacy removed] Product Registration Cyanamid Crop Protection RIPCORD Data Chemical and Physical Properties of Technical , DACO: 0.8
1636430	1996, [Privacy removed] RIPCORD Technical Insecticide Product Chemistry, DACO: 2.99
1636433	1996, [Privacy removed] Final Report CYANAMID RIPCORD Technical Insecticide, DACO: 2.99
1791845	1996, [Privacy removed] Cypermethrin (CL 900,051) Product Chemistry Information on the Technical Grade Material for Registration Purposes, DACO: 2.11.
1791848	1996, [Privacy removed] Manufacturing Summary, Description of Starting Materials, and Detailed Production Process Description for the Technical Grade Active Ingredient (TGAI) and Manufacturing Use Product (MP) RIPCORD, Cypermethrin, DACO: 2.11.1,2.11.2,2.11.3

Pest Control Products Act Registration Number 28092

PMRA Document Number	Reference
1261600	2001, Cypermethrin Technical Insecticide Physical And Chemical Properties (Group B), DACO: 2.14.1,2.14.10,2.14.12,2.14.14,2.14.2,2.14.3,2.14.5,2.14.6,2.14.7 CBI
1261599	Manufacturing Summary for Cypermethrin, DACO: 2.11.1 CBI
1261602	2001, Cypermethrin Technical Insecticide Product Identity, Composition and Analysis (Group A) and Confidential Attachment, DACO: 2.11.2,2.11.3,2.11.4,2.12.1 CBI
1261601	2000, Preliminary Analysis Of Five Representative Production Batches Of Cypermethrin Technical Grade Active Ingredient (TGAI) To Determine % Cypermethrin And To Quantify Its Associated Impurities, DACO: 2.13.1,2.13.2,2.13.3 CBI
2410183	2014, PRELIMINARY ANALYSES OF FIVE REPRESENTATIVE PRODUCTION BATCHES OF CYPERMETHRIN TECHNICAL GRADE ACTIVE INGREDIENT (TGAI) TO DETERMINE % CYPERMETHRIN AND TO QUANTIFY ITS ASSOCIATED IMPURITIES, DACO: 213.3 CBI
2410191	2014, PRELIMINARY ANALYSES OF FIVE REPRESENTATIVE PRODUCTION BATCHES OF CYPERMETHRIN TECHNICAL GRADE ACTIVE INGREDIENT (TGAI) TO DETERMINE % CYPERMETHRIN AND TO QUANTIFY ITS ASSOCIATED IMPURITIES, DACO: 213.3 CBI

Pest Control Products Act Registration Number 32074

PMRA Document Number	Reference
2438958	2014, Applicant's Name and Office Address, Formulating Plant and address and Trade Name for Sharda Cypermethrin Technical Insecticide, DACO: 2.1,2.2,2.3
2438959	2014, Applicant's Name and Office Address, Formulating Plant and address and Trade Name for Sharda Cypermethrin Technical Insecticide, DACO: 2.1,2.2,2.3 CBI
2438960	2007, Enforcement Analytical Method - Validation of GC-MS and GLC Analytical Methods for Determination of Cypermethrin and its Associated Impurities in Cypermethrin Technical Samples, DACO: 2.13.1
2438961	2007, Appendix 3 for Enforcement Analytical Method - Validation of GC-MS and GLC Analytical Methods for Determination of Cypermethrin and its Associated Impurities in Cypermethrin Technical Samples, DACO: 2.13.1
2438962	2007, Determination of Cis and Trans Isomeric Ratio in Five Representative Production Batches of Cypermethrin Technical Grade Active Ingredient (TGAI), DACO: 2.13.1 CBI
2438963	2007, Preliminary Analysis of Five Representative Production Batches of Cypermethrin Technical Grade Active Ingredient (TGAI) to Determine % Cypermethrin and to Quantify its Associated Impurities, DACO: 2.12.1,2.13.2,2.13.3,2.13.4,2.7,2.8,2.9 CBI
2438968	2008, Determination of Physical Parameters, Storage Stability and Shelf Life Specification Data for Cypermethrin Technical Material Stored at 54 C +/- 2 C for 14 days, in Compliance with Good Laboratory Practice, DACO: 2.12.1,2.14.1,2.14.10,2.14.11,2.14.12,2.14.13, 2.14.14,2.14.15,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,2.16,2.4,2.5,2.6, 830.7000
2438969	2014, Sharda Worldwide Exports Pvt. Ltd, DACO: 2.11.1,2.11.2,2.11.3,2.11.4 CBI
2506234	2015, Method Validation Clarifications for Sharda Cypermethrin Technical Insecticide, DACO: 2.13.1
2506236	2008, [CBI Removed] (for synthesis) MSDS, DACO: 2.11.2 CBI
2506237	2015, [CBI Removed] MSDS, DACO: 2.11.2 CBI
2506238	2015, [CBI Removed] MSDS, DACO: 2.11.2 CBI
2506239	2015, [CBI Removed] MSDS, DACO: 2.11.2 CBI
2506240	2015, [CBI Removed] MSDS, DACO: 2.11.2 CBI
2506241	2014[CBI Removed] MSDS, DACO: 2.11.2 CBI
2506242	2008, [CBI Removed] MSDS, DACO: 2.11.2 CBI
2506243	2008, [CBI Removed] MSDS, DACO: 2.11.2 CBI

2506244	2008, [CBI Removed] MSDS, DACO: 2.11.2 CBI
2506245	1996, [CBI Removed] MSDS, DACO: 2.11.2 CBI
2506246	2015, MANUFACTURING PROCESS OF CYPERMETHRIN, DACO: 2.11.1,2.11.2, 2.11.3,2.11.4 CBI
2506247	2015, declaration letter from the manufacturer regarding batches used in the 5 batch analysis, DACO: 2.13.3 CBI
2506248	2013, [CBI Removed] MSDS, DACO: 2.11.2 CBI

B. Information Considered in the Toxicological Assessment

List of Studies/Information Submitted by Registrant (Unpublished)

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1258261	Hend, R. and Butterworth, S. 1977b. Study Report Number TLGR.0132.77. Shell Toxicology Laboratory and Statistics Unit of the Sittingbourne Research Centre. Unpublished. DACO 4.3.8
1258265	Pickering. 1980. Study No. TLGR.80.143. Tungstall Laboratory, Sittingbourne Research Centre for Shell Research Ltd., London. Unpublished. DACO 4.3.1
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1203067	Glaister, J.R., Gore, C.W., Marasat, G.J., Phillips, C. and Pratt, I. 1980. ICI Study Report No. CTL/P/327. Prepared by Imperial Chemical Industries, Ltd., United Kingdom. Submitted by ICI Americas Inc. Wilmington, Del. CDL:099855-F. Unpublished. DACO 4.3.1
1203067	Buckwell, A., Butterworth, S. and Stevenson, D. 1977. Experiment No. 1112, Study prepared by Shell Research Ltd., Eng., submitted by ICI Americas Inc., Wilmington, DE: CDL:071077-A. Unpublished. DACO 4.3.2
1203057, 1203222	Kalinowski et al. 1982. ICI, Central Toxicology Laboratory, U.K. Report Number CTL/P/703. Dated July, 1982. Unpublished. DACO 4.3.2
1202064, 1203049	Henderson, C. and Parkinson, G. 1981. Report No. CTL/P/588. Prepared by Imperial Chemical Industries, Ltd., England, submitted by ICI Americas, Inc., Wilmington, DEL.; CDL:070564-C. Unpublished. DACO 4.3.5

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1203232	Milburn, G., Banham, P., Birtley, R., et al. 1982. Report No. CTL/P/683. Study prepared by Imperial Chemical Industries PLC, England. Submitted by ICI Americas, Inc., Wilmington, DE; CDL:071074-A; 071075. Unpublished. DACO 4.5.1
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Additional Information Considered

i) Published Information

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2351146	USEPA. 2003a. Review of Cypermethrin Incident Reports. Chemistry and Exposure Branch, HED. DACO 12.5.4

PMRA Document Number	Reference
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2351173	USEPA. 2005. Cypermethrin: Phase 2 HED Risk Assessment for the Eligibility Decision (RED). PC Code 109702; DP Barcode D293415. DACO 12.5.4
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2220437	Cui, Y., Guo, J., Xu, B. and Chen, Z. 2006. Mutat. Res. 604(1-2); 6-41. DACO 4.5.8
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2324424	Puig, M. Carbonell, E., Xamena, N., Creus, A. and Marcos, R. 1989. Mutagenesis 4:72-74. DACO 4.5.6
2220441	Surralles, J., Xamena, N., Creus, A., Catalan, J., Norppa, H., and Marcos, R. 1995. Mutat. Res. 341(3): 169-184. DACO 4.5.5
2220443	Bhunya, S.P. and Pati, P.C. 1988. Toxicol. Lett. 41(3): 223-230. DACO 4.5.7
2220436	Amer, S.M., Ibrahim, A. and El-Sherbeny, K.M. 1993. J. Appl. Toxicol. 13: 341-345. DACO 4.5.7
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2220432	Cantalamessa, F. 1993. Arch. Toxicol. 67: 510-513. DACO 4.2.1
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2220434	McDaniel, K.D. and Moser, V.C. 1993. Neurotoxicology and Teratology. 15:71-83. DACO 4.5.12
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1789382	Freeman, C. 1989. Study Report Number A89-2914. Prepared by FMC Corp., Philadelphia, PA. Dated June 14, 1989. Unpublished. DACO 4.2.1
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1789388	Daly, I. 1994. Study by Pharmaco LSR, Inc., East Millstone, NJ. Lab Report No. 92-3114. Unpublished. DACO 4.3.2
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C. Information Considered in the Dietary Assessment

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PMRA# 1048451 Waiver from the requirement for plant metabolism for Up-Cyde 2.5 EC, United Phosphorus Inc. (UPI). Deficiency response submitted June, 2005.

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